CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 24, 2007

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 22-047 (This overview should be filed with the 07-17-2006 original submission.)

SUBJECT: Recommendation of Approvable Action for quetiapine fumarate extended release (Seroquel® XR) for the Treatment of Schizophrenia

1. BACKGROUND

Quetiapine fumarate (Seroquel®) is an atypical antipsychotic agent. In the U.S., the immediate release (IR) oral formulation of quetiapine was first approved in the treatment of schizophrenia in September 1997. It is also approved for the treatment of bipolar I disorder, acute mania and depression. The oral tablet formulation is available as 25, 50, 100, 200, 300, and 400 mg strength. Quetiapine's efficacy in schizophrenia and bipolar disorder is thought to be mediated through a combination of dopamine D2 and serotonin 5-HT_2 antagonism.

The Division (previously DNDP) met with the sponsor on June 20, 2002 for a pre-NDA meeting. During this meeting, the Division agreed that no preclinical animal data were required for the NDA submission of this formulation. A second pre-NDA meeting scheduled for October 13, 2005, was cancelled after the Division provided preliminary meeting comments agreeing that positive results from either study 132 or 133 supports inclusion of the proposed language in the U.S. label. On April 20, 2006, the Division also provided clarification to the sponsor's pre-NDA questions including a response that results from the PK study regarding switching from IR to XR and one pivotal efficacy study would be sufficient for the NDA filing.

On July 17, 2006, the sponsor has submitted an application for marketing approval of quetiapine sustained release tablets for 50, 200, 300 and 400 mg strengths. The proposed dose range of Seroquel XR in the treatment of schizophrenia is 400-800 mg/day, administered once daily. The result of one pivotal efficacy and safety trial (study 132) was included in this NDA submission.

This NDA has been reviewed by Prafull Shironmani, Ph.D., Chemistry Reviewer, the Office of New Drug Quality Assessment; Sonia Tabacova, Ph.D., Pharmacology/Toxicology Reviewer; Kofi Kumi, Ph.D., Clinical Pharmacologist, the Office of Clinical Pharmacology; and Philip Dinh, Ph.D., Statistical Reviewer, the Office of Biostatistics (review dated 4/2/07). For the clinical review, the efficacy portion was completed by Michelle Chuen, M.D., Medical Officer, DPP and the safety review was completed by Greg Dubitsky, MD., DPP Medical Officer (a joint review dated 04/09/2007). At the time of completion of this memo, the CMC and OCP reviews are not finalized.

2.0 CHEMISTRY

The CMC review has not been finalized yet. At this time, I am not aware of any CMC issues that would preclude an approvable action. The CMC reviewer has provided some preliminary labeling comments that all "sustained release" should be changed to "extended release (XR)."

3.0 PHARMACOLOGY/TOXICOLOGY

There is no new pharmacology/toxicology concern in this submission.

4.0 CLINICAL PHARMACOLOGY

At the time of completion of this memo, final OCP review is still pending. However, based on my communication with Dr. R. Baweja, the OCP team leader, I am not aware of any OCP issues that would preclude an approvable action.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was mainly based on the result of an international, short-term, multi-center, double-blind, double-dummy, randomized, placebo-and active (quetiapine IR) controlled, fixed dose trial (Study 132). The sponsor also conducted two additional efficacy studies that had a similar study design to compare the effects of three doses of quetiapine XR (studies 041 and 133) and both studies are considered to be failed studies.

The sponsor indicated that results of the pivotal clinical study 132 demonstrated that doses of quetiapine XR tested (400, 600, 800 mg) were superior to placebo on the primary efficacy variable. I would briefly describe the results of each of these studies in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

<u>Study 132</u>

This was a 6-week, multi-center, randomized, double-blind, double-dummy, placebo and active-controlled study in adult (age 18-65 yrs) patients meeting DSM-IV criteria for schizophrenia. It's comprised of three periods: screening and enrollment period (Day -7 to 0), randomized and dose escalation period (Day 1 to 6), and fixed dose period (Day 7 to 42) of treatment. Subjects were randomized to either quetiapine XR (at fixed doses of 400, 600 or 800 mg/day), quetiapine IR (at a fixed dose of 400 mg/day), or placebo. At randomization, subjects were outpatients, inpatients or daypatients at a hospital.

The study was conducted at 39 centers in non U.S. sites (South Africa, Russia, Greece, Romania, Bulgaria, India, Indonesia, and Philippines). A total of 665 subjects were screened for this study; 588 were randomized. The ITT samples (N=573) for quetiapine XR (400, 600, 800 mg), quetiapine

IR 400 mg and placebo were 111, 111, 117, 119 and 115, respectively. The subjects enrolled were mostly white, mean age was 34 yrs, and had approximately 40% female subjects. There seemed to be no significant differences in demographic characteristics among the treatment groups and total PANSS scores at baseline as well. A total of 446 subjects (76%) completed the study. The most common reason for early withdrawal was lack of efficacy.

The efficacy assessment included the PANSS and the CGI-S, administered weekly between Day 7 to 28 and at Day 42. The primary efficacy measure was the difference between the baseline and Day 42 (LOCF) in PANSS total score. The primary end point phase was the change in the total score of the PANSS from baseline to the last post-randomization assessment in the double-blind treatment period. The ITT data set included all randomized subjects who received at least one dose of assigned study medication, and had at least one post-baseline efficacy assessment. The LOCF analysis was considered primary, but OC was also done. The ANCOVA was the statistical model employed, with Hommel method was used to adjust the p-values for multiple comparisons. In this study, all three doses (400mg, 600mg, and 800mg) were statistically significantly different from placebo at the .05 level. Doses of quetiapine XR 600mg and 800mg appeared to show additional benefits over XR 400mg where dose XR 600mg and 800mg showed similar results.

Dr. Dinh confirmed the primary efficacy results. He also applied MMRM and OC as sensitivity analyses. Dr. Dinh noted in his review that, regardless of the method used for multiplicity adjustments (Holm's; Hommel's), the results yielded the same conclusion. The results based on the LOCF analysis are as follows:

Efficacy Results on PANSS Total Scores for Study 132 (LOCF):

	Mean Baseline PANSS (SD)	LS Mean Change from Baseline at Day 42	Difference from placebo; p-values (vs. placebo)
Quetiapine XR 400 mg (N=111)	95.9 (13.9)	-24.8	-6.1; p=0.03
Quetiapine XR 600 mg (N=111)	96.8 (14.3)	-30.9	-12.1; p=<0.0001
Quetiapine XR 800 mg (N=117)	97.4 (14.8)	-31.3	-12.5; p=<0.0001
Quetiapine IR 400 mg (N=119)	96.7 (16.0)	-26.6	-7.8; p=0.0045 (unadjusted)
Placebo (N=115)	96.0 (13.1)	-18.8	

Comment: Both Drs. Chuen and Dinh considered this a positive study for quetiapine XR and I agree with them.

Studies 041 and 133

Study 041 and 133 were short-term, randomized, double-blind, parallel-group, placebo and active controlled, fixed dose studies of quetiapine XR in schizophrenia. Study 041 used quetiapine IR 300 and 600 mg as active control. Study 133 used quetiapine IR as active control 800 mg. As can be seen in the table below, these two studies are considered to be failed studies to demonstrate quetiapine XR over placebo in schizophrenia.

PANNS TOTAL SCORE, LS MEAN CHANGE FROM BASELINE AT DAY 42 (LOCF, ITT POPULATION)

Study	QTP XR 300 mg	QTP XR 400 mg	QTP XR 600 mg	QTP XR 800 mg	QTP IR 300 mg	QTP IR 600 mg	QTP IR 800 mg	Placebo
133	NA	-13.8	-16.8	-14.8	NA	NA	-15.0	-12.1
041	-5.0	NA	-13.0	-11.2	-9.4	-7.0	NA	-5.2

5.1.3 Comments on Other Important Clinical Issues

Dose-Response Relationship/ Size of Treatment Effect

The doses included in the positive efficacy study 132 were 400 mg, 600 mg and 800 mg of quetiapine compared to placebo. The treatment effect size as expressed by LS mean change from baseline at Day 42 on PANSS total score was noted to be smaller for 400 mg (-6.1) but similar for 600 mg and 800 mg doses of quetiapine XR compared to placebo; -12.1 and -12.5, respectively .

Subgroup Analyses

Exploratory subgroup analyses were done to detect subgroup interactions on the basis of gender, age (18-39; 40-65) and race. It appeared that there was no difference in treatment effect based on age or gender. Due to relatively small numbers of black patients, there is insufficient information to determine the effect of race on treatment outcome. Dr. Chuen noted in her review that, based on her email communication with Dr. Chen (statistical reviewer), there was no specific center effect on treatment outcome.

Duration of Treatment

There is no data pertinent to the longer-term efficacy of quetiapine XR in schizophrenia in this submission. The sponsor has an ongoing relapse prevention study (study 004) with quetiapine XR or placebo over 1 year. Since this will be considered a required Phase 4 commitment, we should ask the sponsor to provide updated information with final study report submission date.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analysis of study 132 supported the efficacy claim of quetiapine XR for treatment of schizophrenia.

5.2 Safety Data

5.2.1 Satety Database

Dr. Dubitsky's safety review of this NDA was based on the primary safety database comprised of 3 double-blind, placebo-controlled studies in adult patients with schizophrenia. Dr. Dubitsky's safety review also included data from the remaining 18 studies. In the safety evaluable subject populations of these trials, over 1500 subjects were treated with Seroquel XR.

In the completed double-blind studies, there were 6 deaths reported: 3 in Seroquel XR treatment, 2 in Seroquel IR and 1 in placebo group. As Dr. Dubitsky noted, it did not appear that any of these cases could be directly attributed to treatment with quetiapine. Other serious adverse events (SAE) were reported (including schizophrenia, suicidal ideation, suicidal attempt, aggression) in the clinical trials. Dr. Dubitsky also noted in his review that there was no significant difference in the incidence of any of these SAEs between quetiapine XR and placebo.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is approximately twice or more the placebo risk). The AEs for Seroquel XR included dry mouth, somnolence, dizziness, and dyspepsia. The data did not suggest dose dependency for these four AEs. Similar AEs were observed in Seroquel IR group which included dry mouth, somnolence, dizziness, sedation and tachycardia.

5.2.2.2 Abnormal Laboratory Tests

Neutropenia and Agranulocytosis

There was one patient on quetiapine XR 800 mg/day from study 132 experienced agranulocytosis (neutrophil count under 500/mm^3). This 30 yr old female subject was listed as a dropout due to a decreased neutrophil count under dropouts due to laboratory test abnormalities. On day 28, the laboratory tests revealed neutrophil count of 340/mm^3 and a total WBC count of 3,300/mm^3, and the tests repeated on day 33, revealed a low neutrophil count (670/mm^3 and total WBC count of 3,800/mm^3). Study drug was stopped at that point. A third test done on day 34 showed a similarly low neutrophil count (640/mm^3 and total WBC count of 3,200/mm^3) and the patient was withdrawn from the study. No adverse events were otherwise reported. The patient did not return for clinical follow-up. The incidence of moderate neutropenia (neutrophil count $<1.5\times10^9$/L) was the same in the quetiapine SR and IR groups (1.5%) and higher than in the placebo group (0.8%).

Hyperglycemia

The incidence of AEs such as increased blood glucose, increased glycosylated Hb, polydipsia, diabetes mellitus) in placebo-controlled studies showed the quetiapine SR group the same as for placebo and almost identical to the incidence in the quetiapine IR group (0.5%).

Hypercholesterolemia, Hypertriglyceridemia

There was a statistically significant difference for triglyceride level between the treatment groups: 17.9% of quetiapine SR patients versus 5.1% of placebo patients had a triglyceride level of 200 mg/dL or greater ($p<0.0001$). This effect did not demonstrate clear dose-relatedness across the quetiapine SR dose groups: 17.5% at 400mg, 16.6% at 600mg, and 19.4% at 800mg. The proportion of quetiapine IR patients meeting this criterion was almost as high (15.6%). Seroquel XR treated patients had increases from baseline in mean cholesterol and triglycerides of 4% and 15%, respectively compared to decreases from baseline in mean cholesterol and triglycerides of 2% and 6% for placebo treated patients.

Transaminase elevations

Although eight quetiapine SR patients had an ALT elevation greater than three times the upper limit of normal (ULN), the incidence was slightly less than in the placebo group (1.0% versus 1.2%) and no quetiapine SR patient had a bilirubin elevation greater than 1.5 times the ULN.

Hypothyroidism

No patient in the placebo-controlled studies had a clinically significant decreased free thyroxine level (<0.8×LLN) in combination with an increased TSH (>5 mIU/L). In the clinical trials, 0.5% (4/806) of patients on quetiapine XR vs. 0% (0/262) on placebo experienced decreased free thyroxine and 2.7% (21/786) on quetiapine XR vs. 1.2% (3/256) on placebo experienced increased TSH.

5.2.2.3 Weight gain

Overall, a significantly higher proportion of quetiapine XR patients experienced a 7% or greater weight gain during these trials (13.7% versus 6.7%, p-value = 0.02). However, this change did not appear to be dose related. At 400, 600, and 800 mg of quetiapine XR, the fractions of patients meeting this criterion were 13%, 18%, and 11%, respectively. Among the quetiapine XR patients, the highest incidence of substantial weight gain appeared to occur in the two lowest baseline BMI groups (<18.5; 18.5 to <25).

5.2.2.4 Vital signs, ECG data, Orthostatic Hypotension, Syncope, Seizures

Although the incidence of potentially clinically significant orthostatic vital sign findings was consistently higher in the quetiapine XR group compared to placebo, none of these differences was statistically significant. Nine subjects dropped out due to vital sign abnormalities which included 4 subjects (0.4%) due to orthostatic hypotension in quetiapine XR group and none from the placebo group. Syncope was reported in 0.3% (3/951) of the patients treated with quetiapine XR, compared with 0.3% (1/319) on placebo. No subjects in the placebo-controlled trials experienced a QTc value of 500 ms or above. The sponsor has included the incidence rates of these AEs from Seroquel XR in the respective sections of the labeling.

5.2.2.5 Extrapyrimidal Symptoms

The most common EPS-like event was tremor, reported by 2% of all quetiapine SR patients and less than 1% of placebo patients. There was no clear pattern of dose-relatedness. This pattern of events was similar to that observed in the quetiapine IR treatment groups, for which the overall frequency of any EPS-like event was 7.7% (32/414) without evidence of dose-relatedness.

5.2.2.6 Suicidality

The sponsor has assessed the incidence of patients with suicidal behavior/ideation by using the Columbia Suicidality Analysis. A total of 25 patients had events. The overall incidence of suicidal behavior/ideation in the clinical trials was low in quetiapine XR, i.e., 0.6% (6/951) in quetiapine XR treatment group; 0.9% (3/319) in placebo group. There were no statistically significant differences in the relative risk for suicidality between quetiapine XR and placebo group.

5.2.3 Conclusion Regarding Safety of Quetiapine

Overall, this submission revealed safety findings of quetiapine XR consistent with the previously observed safety profile of Seroquel IR. Other safety concerns such as agranulocytosis, hepatic

failure and myocarditis associated with quetiapine treatment from post-marketing data are under review by the safety team and will be followed up accordingly. There are no new safety concerns that would preclude an approvable action.

6.0 WORLD LITERATURE

The sponsor has indicated that they conducted an update to previously submitted literature searches for published articles published from 8/1/2005 through 7/31/2006 pertaining to the safety of quetiapine. The sponsor stated that the results of the literature searches reflect the known safety profile for Seroquel IR and did not highlight any additional issue affecting the safety of Seroquel XR.

7.0 FOREIGN REGULATORY ACTION

I am not aware that this formulation of quetiapine is approved in any other countries at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 study sites (site 501 and 505 in the Philippines). DSI recommended that data from these inspected sites appear acceptable in support of this NDA. Inspectional findings did not raise any major concern on integrity of study data.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified. Our proposed labeling should be included in the action letter.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that Seroquel XR is effective and reasonably safe in the treatment of schizophrenia. I recommend that we issue an approvable action letter with our labeling proposal. We may consider approval of this NDA provided that an agreement is reached between the sponsor and the Agency regarding the language in the labeling, and also contingent on satisfactory response to any CMC or OCP related issues.

Cc: HFD-130/Laughren/Mathis/Chuen/Dubitsky/Updegraff
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/s/

Ni Aye Khin

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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-047
Submission Code	N
Letter Date	July 17, 2006
Stamp Date	July 17, 2006
PDUFA Goal Date	May 17, 2007
Reviewer(s) Name(s)	Michelle M. Chuen, M.D. and Gregory M. Dubitsky, M.D. (Section 7 and Portion of Section 9.4)
Review Completion Date	April 9, 2007
Established Name	Quetiapine Fumarate Sustained-Release Tablets
Trade Name	None
Therapeutic Class	Antipsychotic
Applicant	AstraZeneca UK Limited
Priority Designation	S
Formulation	50, 200, 300, and 400 mg Tablets
Dosing Regimen	400-800 mg/day
Indication	Schizophrenia
Intended Population	Adults with Schizophrenia

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this application be granted approvable status. It is recommended that further information be requested (see section 9.2). Final approval is contingent on satisfactory responses to the concerns conveyed in the approvable letter, satisfactory statistical, CMC, Pharm/Tox, and Biopharm reviews, and mutual agreement on labeling (see section 9.4).

1.1.1 Risk Management Activity

There are no recommendations for risk management beyond those already in the sponsor's proposed labeling and in the undersigned reviewer's comments on the sponsor's proposed labeling. Please see Section 9.4 for further details.

1.1.2 Required Phase 4 Commitments

It is recommended that the sponsor be required to perform at least one adequate and well controlled clinical trial to examine long-term safety and efficacy.

1.1.3 Other Phase 4 Requests

There are no additional recommendations.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

The efficacy of oral quetiapine fumarate sustained-release tablets (hereafter referred to as QTP SR) in the treatment of patients with schizophrenia is based on Study 132, which was a 6-week fixed dose study (400 mg, 600 mg or 800 mg once daily).

The safety of QTP SR is based on Studies 132, 133, and 041, in which safety was evaluated in 951 QTP SR patients and 319 placebo patients. Deaths, serious adverse events and dropouts due to adverse events were examined for the patients and subjects[1] in the remaining eighteen studies

[1] Per a 4/9/07 conversation with Dr. Greg Dubitsky, the number of exposed patients and subjects is unknown.

(studies 036, 037, 086, 118, 001, 003, 097, 008, 087, 098, 109, 145, 146, 115, 116, 4, 13, and 147).

1.2.2 Efficacy

The sponsor has provided evidence from one study (study 132) that supports the claim of short-term efficacy for the use of QTP SR in schizophrenia at doses of 400 mg, 600 mg, and 800 mg once daily. The primary outcome measure in this study was change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment.

1.2.3 Safety

Greg Dubitsky, M.D., clinical reviewer, performed the safety review for this application.

Per a 4/9/07 conversation with Dr. Greg Dubitsky, the total number of patients and subjects who received QTP SR and had safety data in twenty-one trials is unknown. Per the sponsor's submission, over 1500 patients were treated with QTP SR. The clinical review of the safety database for the Seroquel SR development program revealed no findings which were attributable to quetiapine treatment and inconsistent with the previously observed safety profile for Seroquel.

1.2.4 Dosing Regimen and Administration

Study 132 was a fixed dose study of QTP SR that examined doses of 400, 600, and 800 mg/day versus placebo in the treatment of schizophrenia. All three dose groups produced a significant difference over placebo.

Patients were randomized to 400, 600, and 800 mg treatment groups. For all dose groups, dosing for QTP SR began at 300 mg/day for the first day of treatment. For the 600 and 800 mg treatment groups, dosage was increased to 600 mg/day at Day 2. For the 800 mg treatment group, dosage was increased to 800 mg/day at Day 3.

Based on drug/placebo comparisons, there was evidence of a significant treatment effect for the low dose ($p<0.05$), and results at the two higher doses had greater robustness ($p<0.001$), but were similar in magnitude of effect size [LS mean change from baseline of -24.8 (SE=2.5, 95% CI = -29.8 to -19.9), -30.9 (SE=2.5, 95% CI = -35.8 to -26.0), and -31.3 (SE=2.5, 95% CI= -36.1 to -26.4) for 400 mg, 600 mg, and 800 mg, respectively]. There is overlap of the 95% CI's among all three doses. Therefore, there appears to be no advantage of the higher doses (600 and 800 mg) over the lower dose (400 mg).

The sponsor wishes to include language in labeling regarding switching patients from quetiapine fumarate (SEROQUEL), hereafter referred to as QTP IR, to QTP SR at the equivalent total daily dose. In support of this language, they submitted the results of study 146, an international, multicenter (74 centers in 14 countries [in Australia, Europe, Asia, U.S., Africa and Canada]),

double-blind, randomized, parallel group, double-dummy study in outpatients with schizophrenia. This study included a 4-week run-in period to ensure patients were clinically stable (CGI Severity of Illness ≤3 with no changes from enrollment to randomization) and on a stable dose of QTP IR for at least 4 weeks prior to randomization. Patients taking QTP IR 300 to 450 mg/d at enrollment received QTP IR 400 mg/d during the run-in period, patients taking QTP 475 to 650 mg/d received 600 mg/d and patients taking 675 to 800 mg/d received 800 mg/d during the run-in period. Eligible patients were randomized to 6 weeks of treatment with a fixed dose of either the same dose of QTP IR or the same total daily dose of QTP SR at a ratio of 1:2. The primary outcome variable was the proportion of patients who discontinued due to lack of efficacy or whose PANSS total score increased 20% or more from randomization at any visit. The hypothesis was that the proportion of patients in the IR/SR treatment sequence was lower than the proportion of patients in the IR/IR treatment sequence plus 6% (non-inferiority margin). A one-sided non-inferiority test with margin 6% resulted in a p-value of 0.0431, for which a p-value ≤ 0.025 indicates non-inferiority of SR versus IR. Thus, the results of study 146 do not provide evidence for switching patients from QTP IR to QTP SR at the equivalent total daily dose.

1.2.5 Drug-Drug Interactions

Per Greg Dubitsky, M.D., there were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

1.2.6 Special Populations

Age, gender, and race did not appear to significantly affect treatment response as measured by PANSS total score change from baseline at Day 42. The sponsor did not perform a subset analysis to evaluate the effect of baseline severity of illness, as measured by baseline PANSS total score, on treatment response. Please see Section 6.1.4 for further details.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Quetiapine fumarate (SEROQUEL) has been approved for treatment of bipolar disorder (depression and mania) and schizophrenia. QTP SR is a sustained-release formulation of quetiapine being developed as a once-a-day treatment of schizophrenia.

The sponsor is now seeking approval for treatment of adults with schizophrenia with a dosing regimen of 300 to 800 mg/day based on the results of 3 completed short-term fixed-dose clinical studies.

2.2 Currently Available Treatment for Indications

The 23 moieties approved in the U.S. for the treatment of schizophrenia are: chlorpromazine, promazine, prochlorperazine, perphenazine, trifluoperazine, thioridazine, acetophenazine, propiomazine, fluphenazine, piperacetazine, haloperidol, chlorprothixine, thiothixine, mesoridazine, molindone, loxapine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone.

2.3 Availability of Proposed Active Ingredient in the United States

Quetiapine fumarate (SEROQUEL, quetiapine) is a marketed drug which was first approved on September 26, 1997. It has been associated with several safety issues. Among the major safety issues are increased mortality in elderly patients with dementia-related psychosis, suicidality in children and adolescents, clinical worsening and suicidality, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia and diabetes mellitus.

2.4 Important Issues with Pharmacologically Related Products

There are no other important issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

On 8/27/99, the sponsor submitted a proposal for the development of a sustained-release formulation of quetiapine, with the planned NDA supported by pharmacokinetic data (without additional clinical efficacy trials) to demonstrate the bioequivalence of the sustained-release tablets with the approved immediate-release tablets. On 10/21/99, the Agency informed the sponsor that their proposal was insufficient because a) equivalence for AUC would be insufficient, since this would require the assumption that Cmax and Tmax are of no consequence regarding effectiveness and b) the proposed dose range was unclear. The Agency stated that a clinical study to show effectiveness would be required, and that, ideally, an adequate and well controlled clinical trial should be conducted to test for dose range.

On 1/30/01, the sponsor submitted a protocol for the pivotal Study 041.

On 6/20/02, a pre-NDA meeting was held.[2] Clinical issues addressed included the following:
• FDA agreed that no preclinical animal data were required.
• FDA agreed to deferral of pediatric studies of quetiapine SR.

[2] Please note that the information concerning this meeting is taken from the sponsor's submission, because there were no FDA meeting minutes in DFS and, per 3/28/06 emails from the project manager supervisor, Paul David, and project manager, Kimberly Updegraff, such minutes for this meeting are nonexistent.

• FDA stated that the submission should include a comparison of quetiapine SR and IR safety data for the titration period, i.e., for each treatment arm, comparing vital sign measurements and adverse events over the first week.
• FDA agreed that postmarketing safety data does not need to be included in the NDA because postmarketing safety data on the IR formulation is relevant to the SR formulation and FDA already has access to this data through PSURs.
• FDA requested a comprehensive analysis of any effects on glucose levels observed with quetiapine, which should include SAE's, AE's or dropouts related to changes in glucose levels; new onset diabetes cases, categorized by initiation of insulin or oral antidiabetic agents; and instances of worsening of existing cases. Also, FDA stated that the lower limit of the laboratory value range for glucose should be changed from ≤ 40 mg/dL to ≤ 50 mg/dL.
• The sponsor confirmed that ECG data would include calculation of mean changes, and that the Fridericia formula would be used in calculating corrected QT values.
• FDA indicated that the deadline for submission of the 4-month safety update could be extended up to 6 months, if it meant complete unblinded datasets could be provided for the ongoing studies.

On 12/12/02, the sponsor informed the Division that for "business purposes", the NDA would not be filed during the first quarter of 2003.

During a pre-sNDA meeting between FDA and AstraZeneca on 1/14/05 to discuss the Seroquel Bipolar Depression program, AstraZeneca had the opportunity to request FDA input on the SR schizophrenia program. Results from the meeting included the following:
• FDA stated that one positive study in schizophrenia for the controlled release form would suffice.
• FDA stated that deferral of pediatric schizophrenia studies for the CR form pending completion of work with the IR form remains acceptable
• (b) (4)
• In response to the sponsor's inquiry about whether Seroquel SR was an acceptable formulation for relapse prevention to satisfy the outstanding Phase 4 commitment for NDA 20-639, FDA stated that CR may be used rather than IR, but that it must be superseded formally via a letter.

There were no End-of-Phase 2 meetings for schizophrenia.

A 10/11/05 FDA response to pre-NDA briefing documents submitted by the sponsor (the pre-NDA meeting scheduled for 10/13/05 was subsequently cancelled) included the following:
• agreement that positive results from either Study 132 or Study 133 supports inclusion of the proposed language in the US label
• agreement that the requirements of Section 2.7.4.6 of the CTD regarding postmarketing data are not applicable to Seroquel SR

• [redacted] (b) (4)

On 3/20/06, the Agency provided feedback on the SAP for Study 132. Issues included the validity of the Hochberg and Hommel procedures, assessment of the impact of missing data on the primary analysis, dropout patterns and response profiles of the dropouts and the completers after data unblinding, prespecification of the criteria used for the selection of center or country as an independent variable, inclusion of patients given study treatment different from randomized treatment in the primary analysis, and inconsistency in assigning visits (between the last visit window and the other visit windows).

On 4/20/06, FDA provided clarification to its responses to AstraZeneca's pre-NDA questions, including the following:
• Results from the PK study and one pivotal efficacy study are sufficient for filing a claim regarding switching from IR to SR.

This NDA was submitted to the Agency on July 17, 2006. The Filing Meeting was held on January 8, 2007 and it was concluded that this supplement was fileable. The User Fee due date is May 17, 2007.

A 4-Month Safety Update to the NDA was submitted on November 16, 2006.

2.6 Other Relevant Background Information

The undersigned reviewer was unable to locate any information on withdrawal of the product in other countries, or on submission of marketing authorization applications to foreign regulatory agencies.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

An Environmental Assessment was requested since approval of this NDA will likely result in an increase in usage associated with the new dosage form. This assessment was completed by Ruth Ganunis, Ph.D., Chemist, Center for Drug Evaluation and Research, and on January 19, 2007. It was concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places. A Finding of No Significant Impact (FONSI) was recommended.

According to a 3/27/07 email from Prafull Shiromani, Ph.D., Chemistry reviewer, there are some CMC issues for which an Information Request letter is being sent. At the time of completion of this review, her final review was not available.

3.2 Animal Pharmacology/Toxicology

At the time of completion of this review, neither a Pharmacology/Toxicology review nor a draft of the review was available. According to a 3/27/07 email from Sonia Tabacova, Ph.D., Pharmacology/Toxicology Reviewer, there were no significant pharmacology/toxicology concerns.

3.3 Statistical Review and Evaluation

Philip Dinh, Ph.D., is the statistical reviewer for this NDA. His final review is pending at the time of completion of this review. Based on a draft of his review, he has indicated that study 132 suggests that quetiapine sustained release at all three doses are effective in the treatment of schizophrenia.

3.4 DSI Clinical Site Inspections

The Division of Scientific Investigations (DSI) selected 2 sites for inspection; both were from study 132 [site 501 (Dr. Efren Reyes), and site 505 (Dr. Evelyn Belen)]. The results of these inspections were communicated in a Clinical Inspection Summary completed by Sherbet Samuels, R.N., M.P.H., DSI Consumer Safety Officer, with concurrence by Constance Lewin, M.D., M.P.H., DSI Branch Chief, on February 13, 2007. However, observations noted in the Clinical Inspection Summary were based on communications from the field investigator, and DSI stated that an addendum will be generated if conclusions change significantly upon receipt and review of the final Establishment Inspection Report (EIR). Thus, both sites were classified as Pending.

At site 501, 20 subjects' records (67 subjects were randomized) were audited. There were no significant deviations from FDA regulations observed, and data appeared acceptable.

At site 505, 26 records (50 subjects were randomized) were audited. There were no significant deviations from FDA regulations observed, and data appeared acceptable.

Overall, data from these sites appeared to be acceptable for use in support of this NDA, though these observations were based on communications from the field investigator, and the final EIR is pending.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary safety database for QTP SR in the treatment of adult patients with schizophrenia is comprised of studies 132, 133, and 041. Deaths, serious adverse events and dropouts due to adverse events for the remaining eighteen studies (studies 036, 037, 086, 118, 001, 003, 097, 008, 087, 098, 109, 145, 146, 115, 116, 4, 13, and 147) were also examined.

The efficacy of QTP SR in the treatment of adult patients with schizophrenia is based on studies 132, 133, and 041, which were double-blind, double-dummy, randomized placebo- and immediate-release quetiapine (QTP IR)-controlled, parallel-group, fixed-dose trials of about 6 weeks duration.

4.2 Tables of Clinical Studies

A total of twenty-one clinical trials comprise this application. These trials are summarized in the table below.

TABLE 4.2.1: QTP SR STUDIES

Completed Phase I Studies	
Single-Dose	
036	Single-center, open-label, crossover study to assess the comparative bioavailability of QTP IR in fasting state with three 300-mg SR formulations in fasting and fed states in 14 adult patients (8 with schizoaffective disorder, 4 with schizophrenia, and 2 with bipolar disorder)
001	Single-center, open-label, randomized, 5-treatment, 5-period, 4-sequence crossover study to compare the single-dose pharmacokinetics of QTP between 4 SR tablet formulations and an IR tablet in 18 adult patients (17 with schizophrenia and 1 with schizoaffective disorder)
Multiple-Dose	
037	Single-center, open-label, multiple-dose study to compare the bioavailability of QTP from each of 3 SR tablet dose strengths (50 mg SR, 200 mg SR, and 300 mg SR-C) and to assess the relative bioavailability of 300-mg tablets of SR formulations C and D, using a 200-mg IR formulation tablet as the reference in 15 adult patients (8 with schizophrenia, 4 with schizoaffective disorder, and 3 with bipolar disorder)
086	Single-center, open-label, multiple-dose study to evaluate the multiple-dose PK of QTP at 5 dose levels (100 mg, 200 mg, 300 mg, 600 mg, and 800 mg) of SR formulation and to evaluate the effect of food on the bioavailability of SR formulation tablets (200 mg SR and 300 mg SR) in 16 adult patients with

	schizophrenia
118	Multicenter, open-label study to evaluate the steady-state pharmacokinetics of 4 different commercial-scale QTP SR tablets (50 mg, 200 mg, 300 mg, and 400 mg), and to evaluate the effect of food on the bioavailability of 50-mg and 300-mg SR tablets in 30 adult patients (26 with schizophrenia and 4 with schizoaffective disorder)
003	Single-center, open-label, 2-cohort, randomized, 2-treatment, 2 period crossover study to estimate the effect of a light meal on the steady state pharmacokinetics of QTP SR (50 mg and 300 mg) versus the fasting state in 20 healthy adult subjects and 13 adult patients (11 with schizophrenia, 1 with schizoaffective disorder, and 1 with bipolar disorder)
097	Single-center, open-label, randomized, 2-period crossover study to compare the steady-state area under the QTP concentration-time curve across a 24-hour interval of QTP SR with that of QTP IR in 28 adult patients (19 with schizophrenia, 8 with schizoaffective disorder, and 1 with bipolar disorder)
008	Multicenter, double blind, randomized, 2-period crossover study to determine if there is a >10% difference in intolerability between QTP SR and placebo in 63 healthy adult subjects
087	Multicenter, double-blind, double-dummy, randomized, parallel-group study to determine the highest tolerable starting dose (up to 300 mg/day) of QTP SR in 87 adult patients (43 with schizophrenia, 38 with schizoaffective disorder, and 6 with bipolar disorder)
098	Single-center, double-blind, double-dummy, randomized, parallel-group study to determine the tolerable starting dose (400, 600, or 800 mg/day) of QTP SR in 22 adult patients (10 with schizophrenia, 7 with schizoaffective disorder, 4 with bipolar disorder, and 1 unknown)
109	Multicenter, double-blind, randomized, parallel-group study to determine the tolerability of a proposed dose-escalation scheme for QTP SR in 28 patients (22 with schizophrenia and 6 with schizoaffective disorder)
145	Multicenter, double-blind, randomized, parallel-group study to compare the safety and tolerability of 2 dose-escalation schemes using the SR formulation of QTP to the safety and tolerability of a constant dosage strength scheme using the same SR formulation in 52 patients (43 with schizophrenia and 9 with schizoaffective disorder)
115	Multicenter, double-blind, double-dummy, randomized, parallel-group, QTP IR-controlled study to assess the safety and tolerability of QTP SR compared with QTP IR in 100 patients with Alzheimer's disease aged 65 to 94 years
116	Single-center, open-label, multiple-dose study to investigate the steady-state pharmacokinetics of QTP SR in one 15-year-old patient with schizoaffective disorder
Completed Phase 2/3 Studies	
041	U.S. and Canada, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo- and QTP IR-controlled study to demonstrate the

	superior efficacy of QTP SR 300 mg/day, 600 mg/day, and 800 mg/day compared with placebo in 532 patients with schizophrenia over 6 weeks
132	International, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo- and QTP IR-controlled study to demonstrate the superior efficacy of QTP SR 400 mg/day, 600 mg/day, and 800 mg/day compared with placebo in 588 patients with schizophrenia over 6 weeks
133	U.S., multicenter, double-blind, double-dummy, randomized, parallel-group, placebo- and QTP IR-controlled study to demonstrate the superior efficacy of QTP SR 400 mg/day, 600 mg/day, and 800 mg/day compared with placebo in 565 patients with schizophrenia over 6 weeks
146	International, multicenter, double-blind, double-dummy, randomized, parallel-group, QTP IR-controlled study to demonstrate that the efficacy of QTP SR (400 mg/d, 600 mg/d, or 800 mg/d; once daily) is not inferior to that of QTP IR (400 mg/d, 600 mg/d, or 800 mg/d; twice daily) in 630 patients with schizophrenia over 6 weeks, preceded by a 4-week run-in treatment with QTP IR (400 mg/d, 600 mg/d, or 800 mg/d; twice daily)
Ongoing Studies	
004	International, multicenter, randomized, double blind, parallel-group, placebo-controlled Phase III study to evaluate prevention of relapse in patients in stable condition with chronic schizophrenia receiving QTP SR or placebo over 1 year
013	Two-center, Phase I, double blind, randomized, 2-period (1 week each) crossover study to determine if there is a greater than 10 percentage point difference in intolerability between the escalated dosing of QTP SR and placebo
147	International, multicenter, open label, non-comparative study to evaluate the feasibility of switching any antipsychotic treatment to QTP SR in patients with schizophrenia over 12 weeks

4.3 Review Strategy

A listing of the items examined during the course of this review is provided in Table 4.3.1. The study reports for studies 036, 037, 086, 118, 001, 003, 097, 008, 087, 098, 109, 145, 146, 115, 116, and 013 were examined by Greg Dubitsky, M.D. for major safety findings only. Regarding studies 004 and 147, only major safety findings as described in the 4-Month Safety Update were examined by Greg Dubitsky, M.D.

TABLE 4.3.1: ITEMS UTILIZED IN THE REVIEW

Submission Date	Items Reviewed
July 17, 2006	Clinical Study Reports: Studies 041, 132, 133, 036, 037, 086, 118, 001, 003, 097, 008, 087, 098, 109, 145, 146, 115, and 116 Proposed Labeling Financial Disclosure Certification Application Summary Case Report Tabulations (.xpt files)

	Case Report Forms
October 17, 2006	Response to FDA Request
October 25, 2006	Response to FDA Request
November 16, 2006	4-Month Safety Update Integrated Summary Clinical Study Report: 013
March 7, 2007	Errata, updated tables, listings, and datasets: Studies 132, 133, and 146 Clinical Safety Summary Errata, updated tables, and pooled datasets 4-Month Safety Update Errata
March 20, 2007	Proposed Labeling

4.4 Data Quality and Integrity

The efficacy data from the one positive trial was examined by the statistical reviewer, Yeh-Fong Chen, Ph.D., and there were no outliers or sites identified that were felt to be driving the efficacy results. The Division of Scientific Investigations (DSI) chose 2 Philippines sites from study 132 for inspection: Dr. Efren Reyes and Dr. Evelyn Belen. This was based on the number of enrollments. Results of the DSI inspections are described in section 3.4.

Greg Dubitsky, M.D. conducted an audit of adverse event safety data by comparing Case Report Forms (CRF's), Narratives, and adverse event line listings for consistency of adverse event information across these two documents in a random sample of eleven patients. Results are described in section 7.2.8 of this review.

4.5 Compliance with Good Clinical Practices

Studies 041, 132, and 133 were performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference of Harmonization (ICH) and Good Clinical Practice guidelines.

4.6 Financial Disclosures

For purposes of this NDA, all three studies (041, 132 and 133) are considered "covered clinical stud[ies]" in accordance with 21 CFR 54.2 (e).

Among the clinical investigators in these studies, two were identified by the sponsor as having financial arrangements that require disclosure:

(b) (6) received significant payments (in excess of $25,000) from the sponsor for being a lecturer and doing

speaking engagements as part of AstraZeneca's speaker's bureau. It is unlikely that these arrangements biased the study results since (b) (6).

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Three clinical investigator in these trials was identified by the sponsor as not having provided financial disclosure information, and having left the facility with no forwarding address. The investigators were identified as (b) (6) a subinvestigator at site 8 (study 041), (b) (6) a subinvestigator at site 13 (study 041), and (b) (6) a subinvestigator at site 025 (study 041). These sites contributed 9 patients, 8 patients, and 10 patients, respectively, of the 333[4] patients in the study.

5 CLINICAL PHARMACOLOGY

Please note that a Clinical Pharmacology and Biopharmaceutics review was not available at the time of completion of this review, and the information below was obtained from the sponsor's Summary of Clinical Pharmacology Studies. Per a 3/29/07 conversation with Hao Zhu, Ph.D., OCPB reviewer, based on pharmacokinetic data (similar AUC's and Cmax's), the clinical responses of QTP SR and QTP IR are expected to be similar.

5.1 Pharmacokinetics

Quetiapine SR is a sustained-release formulation designed to be administered once daily. Peak plasma quetiapine concentrations (Cmax) occur approximately 6 hours after administration of quetiapine SR (Tmax), compared with approximately 1 hour for the IR formulation. The elimination half-life is approximately 7 hours for both formulations.

Quetiapine SR displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily.

When compared directly to the same total daily dose of quetiapine IR administered in divided doses twice daily to steady state, quetiapine SR administered once daily displays the same area under the plasma concentration-time curve (AUC), and Cmax for quetiapine SR is approximately 13% lower than that observed for the morning dose of quetiapine IR.

[3] Number of patients based on Efficacy MITT
[4] Number of patients based on Efficacy MITT

A high-fat meal (approximately 800 to 1000 calories, with 50% derived from fat content) produced significant increases in Cmax (44% to 52%) and AUC (20% to 22%). In comparison, a light meal (approximately 300 calories, with minimal fat content) had no significant effect on the Cmax or AUC of quetiapine SR.

A fully validated Level A IVIVC model has been successfully developed for the quetiapine SR tablet formulation.

5.2 Pharmacodynamics

A quetiapine SR starting dose of 300 mg/day was well tolerated based on assessments of AEs, vital signs, and ECG findings. A starting dose of 400 mg/day caused unacceptable pulse-rate increases in some patients, and the tolerability of higher starting doses was not investigated. Accordingly, 300 mg/day was selected as the starting dose for the pivotal efficacy and safety studies (Studies 041, 132, and 133).

Dose escalation from 300 mg/day on Day 1 to 600 mg/day on Day 2 and 800 mg/day on Day 3 was well tolerated and was therefore used in the design of the pivotal efficacy and safety studies (Studies 132 and 133). Doses of quetiapine SR studied were as well tolerated as quetiapine IR, despite being initiated at higher doses than quetiapine IR.

Safety assessments for quetiapine SR did not present any new findings from those seen with quetiapine IR in patients with schizophrenia.

Special Studies
Study 008 was conducted to investigate the safety and tolerability of quetiapine SR in healthy volunteers at starting doses of 150 mg with further dose escalation over 8 days. This study was conducted to support the clinical development program for another indication for quetiapine SR.

Quetiapine SR at 150 mg was clinically intolerable compared to placebo in this sample of normal, healthy subjects. In relation to the primary objective of this study, intolerability during quetiapine SR treatment was more than 10 percentage points different from placebo treatment. Most of the difference in tolerability was related to transient orthostasis and syncope events that occurred on the first day of exposure to quetiapine SR, and then attenuated within a day of continued treatment.

The absolute number of syncope and syncope-like intolerability events during treatment with 150 mg quetiapine SR compared with placebo treatment exceeded the pre-defined limits in this study, resulting in a determination of absolute intolerability.

Safety assessments, the secondary objective of this study, were consistent with the known pharmacological effects of quetiapine on nonpsychotic subjects who had not previously received antipsychotic medication. There were no unexpected adverse events on either treatment.

5.3 Exposure-Response Relationships

See Section 8.1 for a discussion of efficacy dose response and Section 7.1.5.6 for a discussion of safety dose response.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This supplemental application seeks to establish the safety and efficacy of quetiapine SR in adult patients with schizophrenia.

6.1.1 Methods

The sponsor has conducted three multicenter studies to evaluate the short term efficacy of quetiapine SR in the treatment of adult patients with schizophrenia.

6.1.2 General Discussion of Endpoints

In a pre-NDA meeting held 6/20/02 (prior to protocol submission for study 132), endpoints were not specifically discussed.

There were no subsequent End-of-Phase 2 meetings for schizophrenia.

In a 10/11/05 response to pre-NDA briefing documents submitted by the sponsor (the pre-NDA meeting scheduled for 10/13/05 was subsequently cancelled), endpoints were not specifically discussed.

On 3/20/06, the Agency provided feedback on the SAP for Study 132 which contained statistical concerns. Issues included the validity of the Hochberg and Hommel procedures, assessment of the impact of missing data on the primary analysis, dropout patterns and response profiles of the dropouts and the completers after data unblinding, prespecification of the criteria used for the selection of center or country as an independent variable, inclusion of patients given study treatment different from randomized treatment in the primary analysis, inconsistency in assigning visits (between the last visit window and the other visit windows). According to a 6/9/06 statistical review by Peiling Yang, Ph.D., the sponsor addressed our concerns except our concern regarding the use of the Hommel procedure as the primary analysis for multiple dose comparisons. Per a 3/28/07 email from Phillip Dinh, Ph.D., statistical reviewer, Study 132 was significant enough that either the Holm or the Hommel procedure would yield the same conclusion.

6.1.3 Study Design

The three pivotal studies (041, 132, and 133) were double-blind, double-dummy, randomized placebo- and immediate-release quetiapine (QTP IR)-controlled, parallel-group, fixed-dose trials of about 6 weeks duration. Study 041 used QTP SR doses of 300, 600, and 800 mg/day and QTP IR doses of 300 and 600 mg/day. Study 132 used QTP SR doses of 400, 600, and 800 mg/day and a QTP IR dose of 400 mg/day. Study 133 used QTP SR doses of 400, 600, and 800 mg/day and a QTP IR dose of 800 mg/day.

These 3 studies will be reviewed separately in Section 10.1.

6.1.4 Efficacy Findings

Predictors of Response
Since Study 132 was the only positive study, it will be the only study discussed in this section. The sponsor performed subset analyses to evaluate the effect of the following variables on treatment response for study 132.

- Age (18-39 vs. 40-65 years old)
- Gender
- Race

Of note, the sponsor did not perform a subset analysis to evaluate the effect of baseline severity of illness, as measured by baseline PANSS total score, on treatment response.

Age, gender, and race did not appear to significantly affect treatment response as measured by PANSS total score change from baseline at Day 42. The appendices in Section 10.4 present data based on these subgroups. Of note, due to relatively small numbers of black patients, there is insufficient information to determine the effect of race on outcome.

Size of Treatment Effect
Treatment effect size was examined in terms of PANSS total score change from baseline at Day 42. Results are summarized in Table 6.1.4.1 below for studies 132, 133, and 041.

TABLE 6.1.4.1: TREATMENT EFFECT SIZE AS EXPRESSED BY PANNS TOTAL SCORE, LS MEAN CHANGE FROM BASELINE AT DAY 42 (LOCF, MITT POPULATION)

Study	QTP SR 300 mg	QTP SR 400 mg	QTP SR 600 mg	QTP SR 800 mg	Placebo
132	NA	-24.8	-30.9	-31.3	-18.8
133	NA	-13.8	-16.8	-14.8	-12.1
041	-5.0	NA	-13.0	-11.2	-5.2

The sponsor has provided evidence from one study that suggests short-term efficacy of QTP SR in schizophrenia (Study 132).

Studies 133 and 041 failed to convincingly demonstrate the superiority of QTP SR over placebo in this condition.

The results of the three studies are summarized in Table 6.1.4.2 below.

TABLE 6.1.4.2: SUMMARY OF EFFICACY RESULTS (STATISTICAL SIGNIFICANCE OF DRUG/PLACEBO DIFFERENCES AT DAY 42 (LOCF, MITT POPULATION)

Variable	Dataset	Study								
		132 400 mg dose	132 600 mg dose	132 800 mg dose	133 400 mg dose	133 600 mg dose	133 800 mg dose	041 300 mg dose	041 600 mg dose	041 800 mg dose
Mean Δ in PANNS total score	LOCF	*	**	**	ns	tr	ns	tr	*	Ns
	OC	**	**	**	ns	ns	ns	NP	NP	NP

Codes: ns= not significant (p>0.10)
tr= trend (0.05<p≤0.10)
* = significant (0.01<p≤0.05)
**= highly significant (p≤0.01)
NP= not provided

Duration of Treatment
No study addressing the long-term efficacy of QTP SR in schizophrenia has been completed.

6.1.5 Clinical Microbiology

Since QTP SR is a solid oral formulation, this section is not applicable.

6.1.6 Efficacy Conclusions

In summary, the sponsor has provided evidence that supports the claim of short-term efficacy for the use of QTP SR in schizophrenia.

7 INTEGRATED REVIEW OF SAFETY

The following safety review was written by Greg Dubitsky, M.D., Clinical Reviewer.

7.1 Methods and Findings

The primary safety database for QTP SR in the treatment of adult patients with schizophrenia is comprised of studies 132, 133, and 041. Deaths, serious adverse events and dropouts due to adverse events for the remaining eighteen studies (studies 036, 037, 086, 118, 001, 003, 097, 008, 087, 098, 109, 145, 146, 115, 116, 4, 13, and 147) were also examined.

Please see Table 4.2.1 for a summary of these investigations.

7.1.1 Deaths

There was a total of six deaths among the studies in the quetiapine SR development program: three in quetiapine SR patients, two in quetiapine IR patients, and one in a placebo patient.[5] All six death cases are summarized below.

One death occurred in the placebo-controlled study 132: Patient E00401029 was a 42 year old male with undifferentiated schizophrenia who died of unknown causes on day 41 of treatment with quetiapine IR 400 mg/day, with the last dose on the previous day. A post-mortem examination was not performed. On day 38, the patient had reported moderate upper abdominal pain without vomiting or diarrhea. Also, on day 28, he was noted to have slightly elevated total WBC and neutrophil counts (14,200/mm^3 and 10,540/mm^3, respectively). The investigator considered the death unrelated to study drug treatment. Further assessment of this case is not possible given the limited available information.

There were two deaths reports in study 115, a safety/ tolerability study in patients with Alzheimer's disease. Patient E0004107 was an 88 year old woman who had been treated with quetiapine SR 300 mg/day and developed pneumonia 28 days after the last dose. She expired the following day. No autopsy was performed. The second death, in Patient E0005305, occurred in an 89 year old male who had been treated with quetiapine IR. He died about nine weeks after his last dose of medication due to deterioration in his general health, which included adenocarcinoma of the prostate with bone metastasis. He had also experienced a complete atrioventricular block in the 30 day period following drug discontinuation.

[5] Please note that serious adverse event information from Phase 1 and Phase 2 trials was submitted by the sponsor on 10-25-06. Information regarding serious adverse events and dropouts due to adverse experiences from the ongoing studies was submitted in the 11-16-06 Four-Month Safety Update.

There was one death during study 4. Patient E1206004 was a 25 year old male who committed suicide by jumping out of a window on day 173 of randomized treatment with placebo.

There were two deaths during study 147. One patient (E3505002) was a 61 year old woman who experienced a cerebrovascular accident on day 76 of treatment with quetiapine SR 400 mg/day. She was hospitalized and quetiapine SR was discontinued on day 83. She died on day 91. Her past medical history was remarkable for only akathisia. Concomitant medications at the time of the event were diazepam 15 mg/day for anxiety and citalopram 40 mg/day for depression.

The second death in study 147 occurred in a 42 year old Oriental female (subject E3803013) with paranoid schizophrenia who had a worsening of psychotic symptoms on day 24 of treatment with quetiapine SR 800 mg/day. Treatment was stopped on day 25 due to lack of therapeutic response and she was withdrawn from the study on day 26, at which time treatment with lorazepam and olanzapine commenced. Citalopram was added on day 29. On day 30 (five days after her last dose of study medication), the patient had collapsed at the nursing home and was being transported to the local medical center when she died. A post-mortem examination was done the next day and the Case Report Form contained the autopsy report, which identified the following as causes of death in the order indicated: a) acute intestinal obstruction and complications, b) severe constipation with impacted stool in large intestines, and c) liver failure.

Reviewer's Comment: The basis for indicating liver failure as a cause of death is unclear. There were no clinical signs or history suggestive of significant liver disease prior to death and histopathology of the liver showed normal liver architecture with portal tracts and a background of diffuse fatty change. Minimal lymphoplasmacytic infiltration was seen in the portal tract with no fibrosis. Regarding the alimentary system, a segment of the terminal ileum was black and gangrenous. There was hard impacted fecal material obstructing the distal part of the large intestine. The wall and mucosa of the gangrenous area was thinned and dilated but no area of perforation was found. Thus, bowel infarction seems a more likely cause of death in this patient than liver failure. Constipation is a common drug-related adverse event associated with quetiapine as well as olanzapine treatment and may have contributed to the development of bowel obstruction and infarction in this patient.

It does not appear that any of the deaths can be directly attributed to treatment with quetiapine.

7.1.2 Other Serious Adverse Events

A serious adverse event was an adverse experience that fulfilled one or more of the following criteria:

- death.
- immediately life-threatening.
- required inpatient hospitalization or prolonged existing hospitalization.
- resulted in persistent or significant disability or incapacity.

• congenital abnormality or birth defect.
• an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the above outcomes.

In the four Phase 3 studies, the most common serious adverse events in the quetiapine SR treatment group were schizophrenia and psychotic disorder. The incidence of these events and other serious events reported by more than one patient in the quetiapine SR treatment group are shown in Table 7.1.2.1 below. For none of these events was the quetiapine SR incidence greater than the placebo incidence to a statistically significant degree (alpha=0.10).

Table 7.1.2.1: Incidence (n(%)) of SAE's Reported By More Than One Quetiapine SR Patient (Phase 3 Study Pool)

Event	Quetiapine SR N=1282	Quetiapine IR N=580	Placebo N=319
Schizophrenia	16 (1.2%)	5 (0.9%)	2 (0.6%)
Psychotic Disorder	11 (0.9%)	4 (0.7%)	3 (0.9%)
Suicidal Ideation	3 (0.2%)	1 (0.2%)	1 (0.3%)
Suicide Attempt	3 (0.2%)	1 (0.2%)	0
Aggression	2 (0.2%)	0	0
Pneumonia	2 (0.2%)	1 (0.2%)	0

Other events classified as serious and reported by one quetiapine SR patient each are as follows: agitation, alcoholism, anxiety, asthma, convulsion, depression, disease progression, dizziness, hematochezia, head injury, toxic hepatitis, hyponatremia, loss of consciousness, major depression, muscle injury, orthostatic hypotension, paranoia, pulmonary embolism, pyrexia, paranoid schizophrenia, thrombosis, and urinary retention. Of these events, two occurrences (toxic hepatitis and loss of consciousness) were examined in more detail and are summarized below. During the placebo-controlled studies, seizures (MedDRA preferred terms of convulsion or grand mal convulsion) were reported in 0.1% (1/951) of quetiapine SR patients and 0.9% (3/319) of placebo patients.

Patient 0052/1208 in study 41 was a 52 year old male in the quetiapine SR 600mg dose group with a history remarkable for dysarthria, hypercholesterolemia, alcoholism, and cholecystectomy. Concomitant medication during the study included flurazepam, lorazepam, docusate sodium, sodium phosphate, erythromycin, chlordiazepoxide, thiamine, and atorvastatin. The patient had stopped drinking in 1990 but, on study day 40, experienced a alcoholic relapse. After consuming 20 beers, he presented to the emergency room and was admitted for detoxification. He was discharged on post-study day 1, after completing the 42 day study treatment. He became ill on post-study day 24 after eating pizza and drinking Pepsi cola and was transported to the emergency room in a weak and confused state. He was diagnosed with toxic hepatitis possibly due to diet and alcoholism. The event resolved on post-study day 31 and the patient was discharged. No further information was available.

Patient 38/E0038015 in study 133 was a 27 year old male in the quetiapine 400mg dose group who experienced unwitnessed loss of consciousness on day 1 of treatment. The patient stated that 10 to 20 minutes after taking his evening dose of study drug, he lost consciousness twice, about five minutes apart and each lasting only a few seconds. His past history was remarkable for chest pain but no syncopal episodes. He presented to the emergency room but did not stay for further evaluation because the events did not reoccur. He stopped study drug and was subsequently withdrawn from the study. At study termination, his vital signs and ECG were unremarkable. Quetiapine has been associated with orthostatic hypotension, sometimes with syncope, during initial dose titration (see Seroquel labeling). Although vital signs at the time of the events were not available, this seems like a plausible, albeit unproven, explanation for these occurrences. In the placebo-controlled studies in this safety database, syncope was reported in 0.3% (3/951) of quetiapine SR patients and 0.3% (1/319) of placebo patients.

In the Phase 1 and Phase 2 studies, there were 14 patients or subjects who had a non-fatal serious adverse event. Eight of these patients were treated with quetiapine SR and the serious experiences were worsening of schizophrenia in five patients and, in one patient each, transient ischemic attack (TIA), dural hemorrhage, and urinary tract infection. The cases of TIA and subdural hemorrhage are summarized below.

Patient 0002/0409 in study 87 was a 57 year old Black male who experienced a transient ischemic attack on day 4 of treatment with quetiapine 300 mg/day, which led to withdrawal from the study. At that time, his speech was slurred and he was shaking, sweaty, and pale. He also complained of nausea and pain in the left side of his chest. Vital signs revealed a blood pressure of 151/100 with a pulse of 87 bpm. He was hospitalized, recovered with treatment, and was discharged the next day. His past medical history was remarkable for hypertension, gout, asthma, arthritis, back surgery, and chronic bronchitis. Concomitant medications were diltiazem, lisinopril, albuterol aerosol, flurbiprofen, acetaminophen, and chloral hydrate. The investigator considered the event unrelated to quetiapine treatment.

Patient 0053/0525 in study 115 was a 78 year old male with Alzheimer's disease who experienced a subdural hemorrhage 12 days after his last dose of study medication, quetiapine SR 300 mg/day. Post-study the patient continued treatment with quetiapine IR. The patient experienced malaise followed by loss of consciousness and, on evaluation, a subdural hemorrhage was confirmed on CT scan. This was probably due to a fall. A hematoma subsequently developed, which was drained and the patient recovered. His medical history was remarkable for hypertensive cardiomyopathy. Concomitant medications included terazosin, which has been associated with thrombocytopenia, and sertraline, a member of the SSRI drug class which has been associated with bleeding tendencies.

With respect to the three ongoing studies in the original submission, in study 147, psychotic disorder and schizophrenia were reported as serious adverse events for five and four patients, respectively, out of the 477 patients in the safety population in this study. Additionally, the following non-fatal serious adverse events were reported as serious events in one patient each:

intestinal obstruction, accidental overdose, aggression, agitation, akathisia, anxiety, breast abscess, extrapyramidal disorder, hand fracture, localized infection, and suicidal ideation.

In sum, there were no serious adverse events that are judged to be unexpected and reasonably attributable to treatment with quetiapine SR.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The overall pattern of dropouts by reason for quetiapine SR and placebo patients in the placebo-controlled study pool is depicted in Table 7.1.3.1.1 below. The overall completion rate for all quetiapine SR groups (62%) was somewhat greater than for the placebo group (57%). The overall dropout incidence was considerably higher in the 300mg group than in the other groups, including placebo. However, this was also the smallest dose group since the 300mg fixed dose was administered in only one of the three studies (study 41) and this study, as will be discussed in section 7.4.1.1, was different from the other two studies in a number of respects. A large proportion of the dropouts in this dose group discontinued treatment due to lack of therapeutic response (about 30%), considerably higher than in the other groups, suggesting that this dose may not be as effective as higher doses. It is also remarkable that there was no apparent dose-response relationship for dropouts due to adverse events. Also, in the highest dose group, the most common reason for dropout was lack of therapeutic response, which was not considerably lower than for the placebo group (15% versus 19%).

Table 7.1.3.1.1: Incidence (%) of Study Completion and Dropouts by Reason and Dose Group Placebo-Controlled Study Pool

	Quetiapine SR					Plac
	300mg N=91	400mg N=227	600mg N=310	800mg N=323	Total N=951	N=319
Completed Treatment	39%	69%	62%	63%	62%	57%
Premature Discontinuation	62%	31%	38%	38%	38%	43%
Eligibility Criteria Not Met	8%	1%	2%	3%	3%	1%
Adverse Event	6%	8%	7%	5%	6%	8%
Lack of Therapeutic Response	30%	8%	12%	15%	14%	19%
Subject Not Willing to Continue Study	13%	9%	11%	9%	10%	10%
Lost to Follow-up	2%	3%	3%	4%	3%	3%
Other Reason	3%	1%	4%	2%	3%	2%

7.1.3.2 Adverse events associated with dropouts

Adverse experiences led to dropout in 6% of all quetiapine SR-treated patients in the placebo-controlled studies. This was only slightly less the incidence of dropout for this reason in the quetiapine IR dose groups (8%) and the placebo group (8%).

No specific adverse event led to dropout in 2% or more of all quetiapine SR patients. Adverse events that led to discontinuation of study treatment in at least 1% of patients in any quetiapine SR dose group in the placebo-controlled studies are presented in Table 7.1.3.2.1 below. The most common events leading to dropout were psychotic disorder and schizophrenia, which likely represented exacerbation of the underlying illness. In general, the patterns of dropouts due to adverse events were very similar for quetiapine SR- and quetiapine IR-treated patients.

Table 7.1.3.2.1: Adverse Events Leading to Dropout in ≥1% of Patients in Any Quetiapine SR Dose Group Placebo-Controlled Study Pool

AE	Quetiapine SR				Placebo
	300mg N=91	400mg N=227	600mg N=310	800mg N=323	N=319
Psychotic Disorder	0%	3%	2%	<1%	2%
Schizophrenia	0%	2%	1%	1%	1%
Agitation	0%	<1%	1%	<1%	<1%
Anxiety	0%	0%	1%	<1%	0%
Sedation	1%	0%	<1%	<1%	<1%
Orthostatic Hypotension	2%	0%	<1%	0%	0%
Convulsion	1%	0%	0%	0%	0%
Dehydration	1%	0%	0%	0%	0%
Hypotension	1%	0%	0%	0%	0%

7.1.3.3 Other significant adverse events

Enumerations of all dropouts due to adverse experiences were examined for the Phase 1, 2, and 3 studies and for the three ongoing studies to identify any unexpected, clinically important events observed with quetiapine SR exposure.

There was one such event from the Phase 3 studies:

Patient E0402009 in study 132 was a 30 year old female with no history of medical conditions who was treated with quetiapine SR 800 mg/day. No concomitant medication was taken during the trial. On day 28, her laboratory tests revealed agranulocytosis (neutrophil count of 340/mm^3 and a total WBC count of 3,300/mm^3). The result was received on day 30 and, on day 31, the test was repeated while quetiapine SR was continued. That result, received on day 33, also

revealed a low neutrophil count (670/mm^3 and total WBC count of 3,800/mm^3). Study drug was stopped at that point. A third test done on day 34 showed a similarly low neutrophil count (640/mm^3 and total WBC count of 3,200/mm^3) and the patient was withdrawn from the study. No adverse events were otherwise reported. The patient did not return for clinical follow-up.

From the ongoing studies, there were an additional two dropouts due to decreased neutrophil counts during study 4 (the relapse prevention study in schizophrenia). These cases are briefly summarized below based on my review of the Case Report Forms.

Patient E1208012 – this 39 year old female with no previous medical conditions was found to have neutropenia (960/mm^3) with a decreased total WBC count (3,100/mm^3) after approximately three months of treatment with quetiapine SR 800 mg/day. Counts remained low about three weeks later, when study medication was discontinued. About one week after stopping drug, counts returned to the low end of the normal range, with a neutrophil count of 2,330/mm^3 and total WBC count of 4,100/mm^3.

Patient E1305001 – this 32 year old male with a history of rheumatoid arthritis and head trauma was found to have a deceased absolute neutrophil count (1,260/mm^3) and total WBC count (3,400/mm^3) after about three and one-half months of treatment with quetiapine SR, mostly at a dose of 800 mg/day. The ANC had been below normal range for about two months prior to this but always greater than 1,500/mm^3. Study medication was stopped and on follow-up about two weeks later, both counts had normalized, with a neutrophil count of 2,730/mm^3 and total WBC count of 4,800/mm^3.

The case from study 132 did meet the criterion for agranulocytosis by neutrophil count (i.e., a neutrophil count less than 500/mm^3) on one occasion, although the neutrophil count increased by a factor of two while the patient continued quetiapine SR, depression of the total WBC counts was only moderate, and there were no known clinical manifestations. The final outcome of that case is unknown due to lack of follow-up. Neither of the study 4 cases progressed to agranulocytosis and both normalized after stopping quetiapine SR therapy. It is notable that all three cases of neutropenia occurred with high-dose quetiapine SR (800 mg/day). According to Seroquel labeling, leukopenia was frequently reported during previously conducted premarketing trials and reports of leukopenia/neutropenia were received during the postmarketing period for Seroquel. Labeling advises the prescriber to consider discontinuing Seroquel if low white blood cell counts develop in a patient. Similar labeling should apply to this formulation, if approved.

7.1.4 Other Search Strategies

7.1.4.1 Search for Extrapyramidal Symptoms

The sponsor searched the adverse experiences reported in the placebo-controlled study pool to identify those coded to one of the following MedDRA terms related to extrapyramidal symptoms (EPS): akathisia, akinesia, athetosis, bradykinesia, buccoglossal syndrome, cervical spasm,

chorea, choreoathetosis, cogwheel rigidity, drooling, dyskinesia, esophageal dyskinesia, dystonia, extrapyramidal disorder, freezing phenomenon, festinating gait, grimacing, hyperkinesia, hypertonia, hypokinesia, masked facies, micrographia, movement disorder, involuntary muscle contractions, muscle rigidity, nuchal rigidity, oculogyration, opisthotonus, parkinsonian gait, parkinsonism, pleurothotonus, posturing, psychomotor hyperactivity, restlessness, tardive dyskinesia, torticollis, tremor.

The proportions of quetiapine SR and placebo patients reporting these events in this study pool are displayed in Table 7.1.4.1.1 below. The most common EPS-like event was tremor, reported by 2% of all quetiapine SR patients and less than 1% of placebo patients. There was no clear pattern of dose-relatedness. This pattern of events was similar to that observed in the quetiapine IR treatment groups, for which the overall frequency of any EPS-like event was 7.7% (32/414) without evidence of dose-relatedness.

Table 7.1.4.1.1: Adverse Events Associated with EPS Placebo-Controlled Studies

MedDRA Preferred term[a]	PLA N=319 n (%)	QTP SR 300 mg N=91 n (%)	QTP SR 400 mg N=227 n (%)	QTP SR 600 mg N=310 n (%)	QTP SR 800 mg N=323 n (%)	QTP SR Total N=951 n (%)
Any adverse events[b]	15 (4.7)	9 (9.9)	10 (4.4)	25 (8.1)	27 (8.4)	71 (7.5)
Tremor	3 (0.9)	1 (1.1)	3 (1.3)	9 (2.9)	6 (1.9)	19 (2.0)
Akathisia	4 (1.3)	0	3 (1.3)	7 (2.3)	7 (2.2)	17 (1.8)
Restlessness	2 (0.6)	2 (2.2)	2 (0.9)	2 (0.6)	9 (2.8)	15 (1.6)
Extrapyramidal disorder	5 (1.6)	1 (1.1)	2 (0.9)	4 (1.3)	4 (1.2)	11 (1.2)
Dystonia	0	2 (2.2)	0	2 (0.6)	1 (0.3)	5 (0.5)
Drooling	0	0	0	1 (0.3)	2 (0.6)	3 (0.3)
Dyskinesia	1 (0.3)	1 (1.1)	1 (0.4)	1 (0.3)	0	3 (0.3)
Muscle rigidity	0	0	0	2 (0.6)	0	2 (0.2)
Tardive dyskinesia	1 (0.3)	1 (1.1)	0	0	1 (0.3)	2 (0.2)
Cogwheel rigidity	1 (0.3)	0	0	1 (0.3)	0	1 (0.1)
Hypertonia	0	1 (1.1)	0	0	0	1 (0.1)
Movement disorder	0	0	0	1 (0.3)	0	1 (0.1)
Parkinsonism	0	0	0	0	1 (0.3)	1 (0.1)
Oculogyration	0	0	0	0	0	0
Parkinsonian gait	1 (0.3)	0	0	0	0	0
Psychomotor hyperactivity	0	0	0	0	0	0

Another method of examining the occurrence of extraypramidal symptomatology is via mean changes from baseline to end of treatment in the Simpson Angus Scale (SAS) and the Barnes Akathisia Rating Scale (BARS). The results of these analyses for the pool of placebo-controlled studies are cited by the sponsor in proposed labeling and are provided in Table 7.1.4.1.2 below for reference. Mean changes were similar across all three treatment groups for both scales.

Table 7.1.4.1.2: Mean Change from Randomization to End of Treatment in the SAS and BARS Total Scores			
	Quetiapine SR	**Placebo**	**Quetiapine IR**
SAS Score			
N	924	307	396
Randomization	1.68	1.52	1.80
End of Treatment	1.02	0.96	1.22
Mean Change	-0.66	-0.56	-0.58
Median Change	0.00	0.00	0.00
BARS Score			
N	925	307	397
Randomization	0.35	0.32	0.42
End of Treatment	0.23	0.21	0.28
Mean Change	-0.12	-0.12	-0.14
Median Change	0.00	0.00	0.00

In the pool of studies 132 and 133, both of which used a similar dose titration schedule, the overall incidence of anticholinergic medication use, often considered as a marker of EPS incidence and severity, was roughly comparable across treatment groups: 2.9% for quetiapine SR, 4.6% for quetiapine IR, and 3.4% for placebo.

7.1.4.2 Search for Glucose Dysregulation

The sponsor searched the adverse experiences reported in the placebo-controlled studies to identify events coded to one of the following MedDRA terms related to diabetes mellitus: anti-insulin antibody increased, anti-insulin antibody positive, blood glucose abnormal, blood glucose fluctuation, blood glucose increased, blood insulin abnormal, blood insulin decreased, blood insulin increased, blood insulin C-peptide abnormal, blood insulin C-peptide decreased, blood insulin C-peptide increased, blood proinsulin abnormal, blood proinsulin decreased, blood proinsulin increased, dawn phenomenon, diabetes mellitus, diabetes mellitus inadequate control, diabetes mellitus insulin dependent, diabetes mellitus non-insulin dependent, diabetes with hyperosmolarity, diabetic coma, diabetic complication, diabetic hyperglycemic coma, diabetic hyperosmolar coma, diabetic hyperosmolar non-ketoacidosis, diabetic ketoacidosis, diabetic ketoacidotic hyperglycemic coma, glucose tolerance decreased, glucose tolerance impaired, glucose tolerance test abnormal, glucose urine present, glycosylated hemoglobin increased, hyperglycemia, hyperinsulinemia, hyperinsulinism, impaired fasting glucose, impaired insulin secretion, increased insulin requirement, insulin resistance, insulin resistance syndrome, insulin resistant diabetes, insulin-requiring type 2 diabetes mellitus, insulin tolerance test abnormal, metabolic disorder, Somogyi phenomenon, polydipsia, polyuria, thirst, blood ketone body

present, blood ketone body increased, neonatal diabetes mellitus, glycosuria during pregnancy, gestational diabetes, glucose tolerance impaired in pregnancy, diabetes complicating pregnancy.

The incidence of these events is provided in Table 7.1.4.2.1 below. The incidence of any of these events in the quetiapine SR group is the same as for placebo and almost identical to the incidence in the quetiapine IR group (0.5%). Except for polyuria, which is not specific for diabetes, other events were reported by only one patient each.

Table 7.1.4.2.1: Adverse Events Associated with Diabetes Mellitus Placebo-Controlled Studies

MedDRA Preferred term[a]	PLA N=319 n (%)	QTP SR 300 mg N=91 n (%)	QTP SR 400 mg N=227 n (%)	QTP SR 600 mg N=310 n (%)	QTP SR 800 mg N=323 n (%)	QTP SR Total N=951 n (%)
Any adverse events[b]	2 (0.6)	1 (1.1)	1 (0.4)	2 (0.6)	2 (0.6)	6 (0.6)
Polyuria	0	1 (1.1)	0	0	1 (0.3)	2 (0.2)
Blood glucose increased	1 (0.3)	0	0	0	1 (0.3)	1 (0.1)
Glycosylated haemoglobin increased	0	0	0	1 (0.3)	0	1 (0.1)
Hyperglycaemia	0	0	0	1 (0.3)	0	1 (0.1)
Polydipsia	0	0	1 (0.4)	0	0	1 (0.1)
Diabetes mellitus	1 (0.3)	0	0	0	0	0
Thirst	0	0	0	0	0	0

7.1.4.3 Search for Neutropenia and Agranulocytosis

To search for adverse experiences representing neutropenia and agranulocytosis, the sponsor searched on the following MedDRA terms: band neutrophil count decreased, band neutrophil percentage decreased, febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count decreased, neutrophil percentage decreased, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutrophil count abnormal, neutrophil percentage abnormal, agranulocytosis.

Only one patient (in the quetiapine SR 800mg group in study 132) was identified through this search: Patient E0402009 in study 132 dropped out for this abnormality and is described under section 7.1.3.3 above.

7.1.4.4 Search for Suicidality

The placebo-controlled trials were searched by the sponsor for the following MedDRA terms suggestive of suicidal ideation or behavior: completed suicide, intentional self-injury, self-injurious behavior, self-injurious ideation, suicide attempt, suicidal ideation.

The incidence of these identified adverse events is displayed in Table 7.1.4.4.1 below. The overall incidence of these events is about the same for quetiapine SR- and placebo-treated patients, 0.8% and 0.9%, respectively, and only slightly higher for quetiapine IR (1%). There is no apparent dose-relatedness for these events. For specific events, the incidence was consistently low across all quetiapine SR treatment groups and placebo.

Table 7.1.4.4.1: Adverse Events Related to Suicidality
Placebo-Controlled Study Pool

MedDRA Preferred term[a]	PLA N=319 n (%)	QTP SR 300 mg N=91 n (%)	QTP SR 400 mg N=227 n (%)	QTP SR 600 mg N=310 n (%)	QTP SR 800 mg N=323 n (%)	QTP SR Total N=951 n (%)
Any adverse events[b]	3 (0.9)	1 (1.1)	3 (1.3)	2 (0.6)	2 (0.6)	8 (0.8)
Suicidal ideation	3 (0.9)	0	2 (0.9)	1 (0.3)	1 (0.3)	4 (0.4)
Intentional self-injury	0	1 (1.1)	0	0	1 (0.3)	2 (0.2)
Suicide attempt	0	0	1 (0.4)	1 (0.3)	0	2 (0.2)

Additionally, AstraZeneca conducted an in-house review of all suicidal behavior and ideation in the four Phase 3 studies following a process developed by a group at Columbia University under the leadership of Dr. Kelly Posner. Specifically, a group of AstraZeneca medical staff (N=3) trained in psychiatry but not associated with the quetiapine SR program were selected and trained in the Columbia review process to assess and categorize the adverse events for patients in studies 41, 132, 133, and 146 under blinded conditions. Adverse event data from these trials were searched utilizing the following search strings:

• for preferred terms: suic, overdos.
• for verbatim terms: accident, attempt, cut, gas, hang, hung, jump, mutilat, overdos, self damag, self harm, self inflict, injur, shoot, slash, suic.

In addition, all events classified as serious, according to the protocol definition, were included as potential suicidal events.

Each identified event had a masked narrative prepared and each narrative was reviewed by three reviewers, who were apprised of the reconciliation process in case of discordant evaluations.

A total of twenty-five patients had events that required review and classification. The results for the quetiapine SR and placebo groups in the placebo-controlled studies are shown in Table 7.1.4.4.2 below. Incidence in the quetiapine IR-treated patient overall was slightly higher, with a 1% incidence of suicidal behavior/ideation (and suicidal ideation).

Table 7.1.4.4.2: Incidence of Suicidal Behavior/Ideation Using the Columbia Review and Classification Process
Placebo-Controlled Studies

	PLA N=319	QTP SR 300 mg N=91	QTP SR 400 mg N=227	QTP SR 600 mg N=310	QTP SR 800 mg N=323	QTP SR Total N=951
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Suicidal behavior/ideation (1, 2, 3, 4)	3 (0.9)	0	3 (1.3)	2 (0.6)	1 (0.3)	6 (0.6)
Suicidal behavior (1, 2, 3)	1 (0.3)	0	1 (0.4)	1 (0.3)	0	2 (0.2)
Suicidal ideation (4)	2 (0.6)	0	2 (0.9)	1 (0.3)	1 (0.3)	4 (0.4)
Possible suicidal events (5, 6, 9)[a]	2 (0.6)	0	0	1 (0.3)	0	1 (0.1)

[a] Includes "intent unknown" and "not enough information" ratings.

The sponsor then computed the relative risk (and 95% confidence intervals) for suicidality after combining the relatively small quetiapine SR 300mg group with the 400mg group. The results are presented in Table 7.1.4.4.3 below. There were no statistically significant differences between quetiapine SR and placebo in the relative risk for suicidality.

Table 7.1.4.4.3: Relative Risk of Suicidal Behavior/Ideation
Placebo-Controlled Studies

	QTP SR 300,400 mg vs Placebo		QTP SR 600 mg vs Placebo		QTP SR 800 mg vs Placebo	
Classification (codes)	Relative risk estimate	95% confidence interval	Relative risk estimate	95% confidence interval	Relative risk estimate	95% confidence interval
Suicidal behavior/ ideation(1, 2, 3, 4)	1.00	0.204, 4.933	0.69	0.115, 4.078	0.33	0.034, 3.148
Suicidal behavior/ ideation(1, 2, 3, 4) + possible suicidal behavior/ ideation (5, 6, 9)	0.60	0.145, 2.497	0.62	0.149, 2.562	0.20	0.023, 1.681

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the three placebo-controlled trials, adverse events were collected from spontaneous reports from the patient, patient reports after prompting with a general question, and observations by the study staff. Symptom checklists were not employed.

Adverse event information was collected on the following study days in addition to the time of randomization:

- study 41 – days 4, 8, 15, 28, and 42.
- study 132 – days 7, 14, 21, 28, and 42.
- study 133 – days 5, 7, 14, 21, 28, and 42.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse event terms used by the study investigators to describe adverse experiences in studies 132 and 133 were coded to MedDRA terminology. For study 41, adverse events were described using COSTART terminology; however, for purposes of comparing these data with those from the other studies and pooling information, these events were then converted to MedDRA terms. MedDRA version 8.1 was utilized for coding adverse event terms.

In order to ascertain the acceptability of the adverse event coding in the placebo-controlled database, the adverse event datasets (.xpt files) for studies 41, 132, and 133 were examined. In particular, the event terms from the CRF (the variables AETEXT for studies 132 and 133 and ADE for study 41) were compared to the MedDRA preferred term (variable PT_NAME for all three studies) for each event listed in the dataset in each of the three studies. This process was performed twice, once after sorting by CRF term and once after sorting by preferred (coded) term. This audit revealed no significant deficiencies in the coding process, which was judged to be acceptable.

7.1.5.3 Incidence of common adverse events

For purposes of identifying the adverse experiences commonly observed with quetiapine SR, the pool of placebo-controlled studies (41, 132, and 133) was examined in terms of the proportions of patients in each treatment group (quetiapine SR and placebo) who reported specific events by MedDRA preferred term.

7.1.5.4 Common adverse event tables

Table 7.1.5.4.1 below presents the incidence for those events reported by at least 2% of all quetiapine SR patients in the pool of placebo-controlled studies.

Table 7.1.5.4.1: Common Adverse Events (events reported by ≥2% of quetiapine SR patients) Placebo-Controlled Studies

MedDRA Preferred Term	Quetiapine SR N=951	Placebo N=319
Sedation	13%	7%
Dry Mouth	12%	1%
Somnolence	12%	4%
Dizziness	10%	4%
Headache	10%	15%
Insomnia	7%	14%
Orthostatic hypotension	7%	5%
Constipation	6%	5%
Nausea	5%	7%
Dyspepsia	5%	2%
Agitation	4%	5%
Heart rate increased	4%	1%
Vomiting	3%	4%
Fatigue	3%	2%
Tachycardia	3%	<1%
Hypotension	3%	<1%
Anxiety	2%	<1%
Weight increased	2%	2%

7.1.5.5 Identifying common and drug-related adverse events

Common and drug-related adverse events are typically defined as those occurring in at least 5% of active drug patients at an incidence at least twice that in the placebo group.

Applying this definition to the above data, the following four events are considered common and drug-related (quetiapine SR incidence, placebo incidence):

- dry mouth (12%, 1%).
- somnolence (12%, 4%).
- dizziness (10%, 4%).
- dyspepsia (5%, 2%).

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 Dose-Dependency of Common Adverse Events

The incidence of the above identified common, drug-related adverse events by randomized quetiapine SR dose group in the pool of placebo-controlled studies is shown in Table 7.1.5.6.1.1 below. Note that, given the proximity of the 300mg dose to the 400mg dose and the considerably smaller size of the 300mg group (N=91) compared to the other groups, the 300mg dose, which was studied only in study 41, has been omitted here.

Table 7.1.5.6.1.1: Adverse Event Incidence by Dose Group Placebo-Controlled Study Pool (excl. 300mg group)

	Quetiapine SR Dose Group		
	400mg N=227	**600mg N=310**	**800mg N=323**
Dry mouth	12%	13%	12%
Somnolence	12%	12%	13%
Dizziness	9%	12%	8%
Dyspepsia	5%	5%	4%

These data do not suggest dose-dependency for these four adverse events.

7.1.5.6.2 Demographic Interactions with Adverse Events

For each of the common, drug-related adverse events identified above, the incidence of these events in the placebo-controlled study pool, stratified by age, gender, and race subgroups, is displayed in Table 7.1.5.6.2.1 below. The sponsor states that there were no important differences in event incidence between these subgroups for these events. However, it should be noted that no results of formal statistical testing were provided and the sponsor's methodology for evaluating these data is unknown.

Table 7.1.5.6.2.1: Effect of Demographic Variables on Adverse Event Incidence Placebo-Controlled Study Pool

Event	Demo. Var.	Subgroup	Quetiapine SR (n/N(%))	Placebo (n/N(%))
Dry Mouth	**Age**	**18-39**	41/509(8%)	3/179(2%)
		40-65	74/442(17%)	1/140(<1%)
	Gender	**Male**	86/670(13%)	2/216(<1%)
		Female	29/281(10%)	2/103(2%)
	Race	**White**	51/462(11%)	2/145(1%)
		Black	50/307(16%)	1/101(1%)

		Oriental	6/134(5%)	0/46(0%)
		Hispanic	4/24(17%)	0/11(0%)
		Other	4/24(17%)	1/16(6%)
Somnolence	**Age**	**18-39**	53/509(10%)	7/179(4%)
		40-65	62/442(14%)	5/140(4%)
	Gender	**Male**	74/670(11%)	9/216(4%)
		Female	41/281(15%)	3/103(3%)
	Race	**White**	49/462(11%)	8/145(6%)
		Black	41/307(13%)	1/101(1%)
		Oriental	18/134(13%)	1/46(2%)
		Hispanic	4/24(17%)	1/11(9%)
		Other	3/24(13%)	1/16(6%)
Dizziness	**Age**	**18-39**	42/509(8%)	3/179(2%)
		40-65	51/442(12%)	9/140(6%)
	Gender	**Male**	48/670(7%)	10/216(5%)
		Female	45/281(16%)	2/103(2%)
	Race	**White**	40/462(9%)	6/145(4%)
		Black	32/307(10%)	3/101(3%)
		Oriental	14/134(10%)	1/46(2%)
		Hispanic	3/24(13%)	0/11(0%)
		Other	4/24(17%)	2/16(13%)
Dyspepsia	**Age**	**18-39**	23/509(5%)	2/179(1%)
		40-65	21/442(5%)	5/140(4%)
	Gender	**Male**	25/670(4%)	4/216(2%)
		Female	19/281(7%)	3/103(3%)
	Race	**White**	23/462(5%)	2/145(1%)
		Black	15/307(5%)	3/101(3%)
		Oriental	3/134(2%)	0/46(0%)
		Hispanic	0/24(0%)	2/11(18%)
		Other	3/24(13%)	0/16(0%)

However, my visual inspection of these data does reveal three differences of potential importance. I computed the odds ratios for these events in each stratum:

• older patients were at higher risk for dry mouth than younger patients (odds ratios of 27.95 and 5.14, respectively).
• females appeared to be at greater risk for dizziness than males (odds ratios of 9.63 versus 1.59, respectively).
• younger patients were at higher risk for dyspepsia than older patients (odds ratios of 4.19 and 1.35, respectively).

Mantel-Haenszel chi-square testing revealed a significant effect of age on dry mouth and gender on dizziness (p-values <0.001 for both). But the effect of age on dyspepsia was not statistically significant (p=0.0827). The clinical importance of these findings is unknown, however, since patients were not randomized on demographic variables and these results have not been replicated in an independent dataset.[6]

7.1.5.6.3 Comparison of Common Adverse Events with Quetiapine SR versus Quetiapine IR

The same criteria for common and drug-related adverse events (occurring in at least 5% of active drug patients at an incidence at least twice that in the placebo group) was applied to the pool of the quetiapine IR treatment groups in the placebo-controlled studies.

Based on this definition, the following six events are considered common and drug-related among quetiapine IR-treated patients (quetiapine IR incidence, placebo incidence):

- sedation (16%, 7%).
- dry mouth (9%, 1%).
- somnolence (13%, 4%).
- dizziness (9%, 4%).
- tachycardia (6%, <1%).

A side-by-side comparison of the common and drug-related adverse experiences with quetiapine SR versus quetiapine IR is provided in Table 7.1.5.6.3.1 below. Overall, there is considerable overlap in the profiles of common, drug-related adverse events.

Table 7.1.5.6.3.1: Common, Drug-Related Adverse Events for Quetiapine SR versus Quetiapine IR

Quetiapine SR	Quetiapine IR
Dry mouth	Dry mouth
Somnolence	Somnolence
Dizziness	Dizziness
Dyspepsia	Sedation
	Tachycardia

7.1.6 Less Common Adverse Events

A listing of all adverse events from the placebo-controlled studies, regardless of reporting frequency, was examined to identify any that might be potentially clinically important and

[6] The Seroquel (IR) NDA did not detect any clinically meaningful effects of demographic variables on adverse event occurrence, according to Seroquel labeling.

possibly related to quetiapine SR or quetiapine IR treatment.[7] After excluding cases of serious adverse events which are discussed above in this review (i.e., death, toxic hepatitis, and convulsions), there were only two such events identified:

• delirium – reported in one quetiapine SR patient who received 300 mg/day (E0140058 in study 41). Since this event was not classified as serious and did not lead to dropout, limited information is available. The investigator description of the event was "delerium" and it was rated as moderate in severity. The precise nature and circumstances of the event are unknown.
• thrombosis – reported in one quetiapine SR patient who had received 600 mg/day for about 41 days (0010/1028 in study 41). He completed the trial and 16 days after his last dose of study drug, he experienced symptoms of a left leg blood clot and subsequently underwent popliteal-to-popliteal vein bypass surgery. The event was classified as serious but was not judged to be related to the study treatment by the investigator.

Other, generally less serious, adverse events identified in this listing which are considered probably related to quetiapine SR treatment are as follows: heart rate increased, hypotension, weight increased, tremor, akathisia, increased appetite, blurred vision, postural dizziness, pyrexia, dysarthria, dystonia, drooling, syncope, tardive dyskinesia, dysphagia, leukopenia, and rash.[8]

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In the three, 6-week, placebo-controlled studies, laboratory testing was conducted as follows:

• study 41 – hematology, hepatic chemistry, thyroid function, prolactin, fasting glucose, and lipid analysis were performed at screening (within seven days of randomization) and at day 42 (or at the time of dropout).
• studies 132 and 133 – clinical chemistry, thyroid function, prolactin, lipids, and urinalysis were done at enrollment and at day 42 (or at the time of dropout). Additionally, chemistry, thyroid function, prolactin, fasting glucose and insulin, lipids, and hematology had to be performed within seven days of randomization or at randomization but prior to first study drug intake. Furthermore, fasting glucose and insulin were assayed at day 28. Note that hematology testing included hemoglobin A1C; this particular assay was also done at day 28.

[7] This examination was based on Table SA-35 in the Summary of Clinical Safety.
[8] Probable drug-relatedness was based on a consideration of the pharmacology of this drug class as well as the drug and placebo incidence rates in this database.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Analyses of laboratory data were examined for the pool of the three placebo-controlled Phase 3 trials (studies 41, 132, and 133). The analyses most helpful in determining whether quetiapine SR was associated with significant abnormalities in laboratory test parameters are the incidence of outliers (i.e., the proportion of patients with clinically important values at any time point) and premature discontinuations due to laboratory abnormalities. Since the evaluation of mean changes from baseline are not suitable for this purpose, only central tendency analyses cited by the sponsor in proposed labeling are presented below.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The following information is proposed by the sponsor for the labeling of this product based on data from the placebo-controlled study pool:

• there was a 4% mean increase in total cholesterol among quetiapine SR-treated patients versus a mean decrease of 2% in the placebo group.
• there was a 14% mean increase in triglyceride levels among quetiapine SR-treated patients versus a mean decrease of 6% in the placebo group.
• there was no substantial difference between quetiapine SR and placebo in the mean change from baseline in serum prolactin levels. Prolactin levels decreased in both treatment groups: -12.96 ng/ml among the quetiapine SR patients (baseline mean of 27.11) and -13.69 ng/ml among the placebo patients (baseline mean of 26.94).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.1.7.2.2.1 below depicts the numbers and percentages of quetiapine SR and placebo patients with potentially clinically important (PCI) values at any time, as defined by the criteria indicated. The number of patients at risk were those who did not meet the specified criterion pre-treatment. Note that glucose and lipid data were obtained under fasting conditions.

Table 7.1.7.2.2.1: Incidence of Potentially Clinically Important Laboratory Values Placebo-Controlled Studies[9]

[9] N_R = number of patients at risk for an abnormality, excluding those meeting the criterion at baseline. N_{PCI} = number of patients meeting the criterion after baseline. $\%_{PCI}$ = percentage of patients at risk who met the criteria after baseline.

Laboratory Test(units)	PCI Criterion	Quetiapine SR			Placebo		
		N_R	N_{PCI}	$\%_{PCI}$	N_R	N_{PCI}	$\%_{PCI}$
Hemoglobin (g/dl)	≤11.5(M)	572	1	0.2	178	2	1.1
	≤10.5(F)	243	6	2.5	88	2	2.3
	≥18.5(M)	576	0	0	178	0	0
	≥16.5(F)	250	0	0	90	0	0
Hematocrit (fraction)	≤0.37(M)	377	5	1.3	114	3	2.6
	≤0.32(F)	126	1	0.8	42	1	2.4
	≥0.55(M)	383	0	0	116	0	0
	≥0.50(F)	129	0	0	44	0	0
RBC's (10^{12} cells/L)	≤3	824	1	0.1	268	1	0.4
	≥6	811	6	0.7	264	1	0.4
Platelets (10^9 cells/L)	≤100	815	2	0.2	261	0	0
	≥600	816	0	0	261	0	0
Leukocytes (10^9 cells/L)	≤3	825	3	0.4	268	1	0.4
	≥16	823	6	0.7	268	2	0.7
Neutrophils (10^9 cells/L)	≤0.5	823	1	0.1	268	0	0
	≤1.5	816	12	1.5	265	2	0.8
	≥10	810	20	2.5	264	6	2.3
Eosinophils (10^9 cells/L)	≥1	806	18	2.2	262	4	1.5
AST (U/L)	≥3×ULN	803	6	0.7	259	1	0.4
ALT (U/L)	≥3×ULN	794	8	1.0	256	3	1.2
AlkPhos (U/L)	≥3×ULN	802	1	0.1	259	0	0
Tot Bilirubin (mg/dL)	≥1.5×ULN	802	0	0	258	2	0.8
Creatinine (mg/dL)	≥1.58	798	3	0.4	259	1	0.4
Sodium (mmol/L)	≤132	791	4	0.5	257	0	0
	≥152	799	0	0	257	2	0.8
Potassium (mmol/L)	≤3	794	1	0.1	256	1	0.4
	≥5.5	788	14	1.8	249	6	2.4
Calcium (mg/dL)	≤8.4	574	9	1.6	191	1	0.5
	≥11.2	578	0	0	194	0	0
Glucose (mg/dL)	≤45	812	1	0.1	264	1	0.4
	≥126	773	67	8.7	254	15	5.9
HbA1C (%)	>7.5	578	4	0.7	194	0	0
Cholesterol (mg/dL)	≥240	718	67	9.3	232	21	9.1
LDL (mg/dL)	≥160	691	47	6.8	227	17	7.5
HDL (mg/dL)	≤40	600	87	14.5	195	23	11.8
Triglycerides (mg/dL)	≥200	659	118	17.9	214	11	5.1
Prolactin (ng/mL)	>20(M)	373	21	5.6	116	8	6.9
	>30(F)	145	18	12.4	48	7	14.6
Free thyroxine	<0.8×LLN	806	4	0.5	262	0	0
TSH(mIU/L)	>5	786	21	2.7	256	3	1.2

On visual inspection of these data, the proportion of quetiapine SR-treated patients with a PCI value was noticeably greater than the corresponding proportion of placebo patients on a number

of laboratory measures: high RBC count, low neutrophil count, high eosinophil count, AST, low serum sodium, low serum calcium, high fasting glucose and Hb1AC, low HDL, high triglyceride levels, free thyroxine, and TSH.

However, the incidence difference was statistically significant, at an alpha level of 0.10, for only one parameter: 17.9% of quetiapine SR patients versus 5.1% of placebo patients had a triglyceride level of 200 mg/dL or greater ($p<0.0001$). This effect did not demonstrate clear dose-relatedness across the quetiapine SR dose groups: 17.5% at 400mg, 16.6% at 600mg, and 19.4% at 800mg. The proportion of quetiapine IR patients meeting this criterion was almost as high (15.6%).

The one quetiapine SR patient from study 132 who experienced agranulocytosis (neutrophil count under 500/mm^3) is discussed under section 7.1.3.3. The incidence of moderate neutropenia (neutrophil count $<1.5\times10^9$/L) was the same in the quetiapine SR and IR groups (1.5%) and higher than in the placebo group (0.8%).

Although eight quetiapine SR patients had an ALT elevation greater than three times the upper limit of normal (ULN), the incidence was slightly less than in the placebo group (1.0% versus 1.2%) and no quetiapine SR patient had a bilirubin elevation greater than 1.5 times the ULN.

No patient in the placebo-controlled studies had a clinically significant decreased free thyroxine level ($<0.8\times$LLN) in combination with an increased TSH (>5 mIU/L). Also, none of these patients experienced hypothyroidism as an adverse event.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were only two dropouts due to laboratory test abnormalities among quetiapine SR-treated patients in the placebo-controlled studies: patient E0402009 in study 132 dropped out due to a decreased neutrophil count and patient E0019010 in study 133 dropped out to due an increase in liver transaminases. Neither case was classified as serious. The former case is discussed in section 7.1.3.3. The latter case occurred in a 41 year old male who was found to have elevated liver enzymes on day 18 of treatment, with an ALT of 170 IU/L and AST of 75 IU/L (values were also elevated pre-treatment: ALT 126 and AST 60 IU/L). Alkaline phosphatase was only slightly elevated (152 IU/L, ULN 145 IU/L) and total bilirubin was normal (0.5 mg/dL; normal range 0.2 to 1.2 mg/dL). This abnormality was ongoing at the time of the report.

No placebo patient dropped out due to a laboratory test abnormality.

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations which would substantially impact on the safety profile of this drug were conducted.

7.1.7.5 Special assessments

No special assessments which would significantly impact on the safety profile of this drug were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured at randomization and each visit in the three placebo-controlled studies, that is, on days 4, 8, 15, 28, and 42 in study 41 and on days 7, 14, 21, 28, and 42 in studies 132 and 133.

Additionally, in study 41, supine and standing vital signs were recorded within 15 minutes before dose administration and 1, 6, and 12 hours after dosing on study days 1, 2, 5, 6, 8, and 9. On day 15, all hospitalized patients had supine and standing vital signs before dosing and 1, 6, and 12 hours post-dose.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The procedure for measuring orthostatic blood pressure was different in study 41 (after 5 minutes of rest, then after 30 seconds or less of standing) versus studies 132 and 133 (after 10 minutes at rest, then 2 minutes of standing). Thus, for orthostatic pulse and blood pressure data, analyses were based on the pool of only 132 and 133.

This review focused on those analyses best suited to identify significant abnormalities in blood pressure, pulse, and body weight, specifically analyses of potentially clinically important outliers and dropouts due to vital sign findings.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Analyses of mean change from baseline in vital sign measurements are not suitable for identifying abnormalities of potential clinical importance and, thus, were not reviewed.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.1.8.3.2.1 below displays the proportions of quetiapine SR and placebo patients who manifested a potentially clinically important (PCI) supine vital sign abnormality at any time. Criteria for PCI values are specified in the table.

Table 7.1.8.3.2.1: Incidence of Potentially Clinically Important Supine Vital Sign Measurements Placebo-Controlled Studies[10]							
Measure (units)	**PCI Criterion**	**Quetiapine SR**			**Placebo**		
		N_R	N_{PCI}	$\%_{PCI}$	N_R	N_{PCI}	$\%_{PCI}$
Pulse (bpm)	>120	930	10	1.1	310	3	1.0
	<50	930	4	0.4	310	4	1.3
	≥15 incr	931	381	40.9	310	98	31.6
	≥15 decr	931	167	17.9	310	75	24.2
Systolic BP (mmHg)	≥180	931	9	1.0	310	2	0.6
	≤90	914	71	7.8	304	21	6.9
	≥20 incr	931	225	24.2	310	82	26.5
	≥20 decr	931	230	24.7	310	70	22.6
Diastolic BP (mmHg)	≥105	931	18	1.9	308	6	1.9
	≤50	928	49	5.3	308	11	3.6
	≥30 incr	931	35	3.8	310	14	4.5
	≥20 decr	931	139	14.9	310	39	12.6

The only notable difference between treatment groups was with respect to the percentage of patients with a 15 bpm or greater increase in supine pulse: 40.9% of quetiapine SR patients and 31.6% of placebo patients met this criterion. This difference is statistically significant (Mantel Haenszel chi-square p-value = 0.003). There is a suggestion that this effect may be dose-dependent: at the 400, 600, and 800mg doses, the proportions of patients meeting this criterion were 29%, 42%, and 45%, respectively. A high proportion of quetiapine IR patients also met this criterion (42.6%).

Based on the pool of data from studies 132 and 133, Table 7.1.8.3.2.2 provides the proportions of patients who met criteria for potentially clinically important orthostatic changes at any time, with PCI changes as defined in the table.

Table 7.1.8.3.2.2: Incidence of Potentially Clinically Important Orthostatic Vital Sign Changes Studies 132 and 133[11]							
Measure (units)	**PCI Criterion**	**Quetiapine SR**			**Placebo**		
		N_R	N_{PCI}	$\%_{PCI}$	N_R	N_{PCI}	$\%_{PCI}$
Pulse (bpm)	**≥20 incr**	619	90	14.5	212	23	10.8
Systolic BP (mmHg)	**≥20 decr**	647	63	9.7	225	17	7.6

[10] N_R = number of patients at risk for an abnormality, excluding those meeting the criterion at baseline. N_{PCI} = number of patients meeting the criterion after baseline. $\%_{PCI}$ = percentage of patients at risk who met the criteria after baseline. Increases or decreases represent changes in the measurement value from the time of randomization.
[11] N_R = number of patients at risk for an abnormality, excluding those meeting the criterion at baseline. N_{PCI} = number of patients meeting the criterion after baseline. $\%_{PCI}$ = percentage of patients at risk who met the criteria after baseline. Increases or decreases represent changes in the measurement value from the time of randomization.

Table 7.1.8.3.2.2: Incidence of Potentially Clinically Important Orthostatic Vital Sign Changes Studies 132 and 133[11]							
Measure (units)	**PCI Criterion**	**Quetiapine SR**			**Placebo**		
		N_R	N_{PCI}	$\%_{PCI}$	N_R	N_{PCI}	$\%_{PCI}$
Diastolic BP (mmHg)	**≥20 decr**	656	24	3.7	226	4	1.8
Combined pulse and systolic BP	**incr pulse ≥20 and decr SBP ≥20**	610	5	0.8	211	1	0.5

Although the incidence of PCI orthostatic vital sign findings was consistently higher in the quetiapine SR group compared to placebo, none of these differences was statistically significant at an alpha level of 0.10.

With respect to changes in body weight, Table 7.1.8.3.2.3 below displays the fractions of study completers, by body mass index at randomization, who exhibited a weight increase of 7% or greater in the placebo-controlled studies.

Table 7.1.8.3.2.3: Incidence of a 7% or Greater Increase in Body Weight from Randomization to End of Treatment Placebo-Controlled Studies (Study Completers)						
BMI (kg/m^2) Category at Randomization	**Quetiapine SR**			**Placebo**		
	N_R	N_{PCI}	$\%_{PCI}$	N_R	N_{PCI}	$\%_{PCI}$
<18.5	41	10	24.4	14	2	14.3
18.5 to <25	220	44	20.0	70	4	5.7
25 to <30	130	9	6.9	31	3	9.7
30 to <40	118	10	8.5	38	1	2.6
≥40	40	2	5.0	10	1	10.0
Total	549	75	13.7	163	11	6.7

Overall, a significantly higher proportion of quetiapine SR patients experienced a 7% or greater weight gain during these trials (13.7% versus 6.7%, p-value = 0.02). However, this change did not appear to be dose related: at 400, 600, and 800mg of quetiapine SR, the fractions of patients meeting this criterion were 13%, 18%, and 11%, respectively. Among the quetiapine SR patients, the highest incidence of substantial weight gain appeared to occur in the two lowest baseline BMI groups.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

An enumeration of dropouts due to vital sign abnormalities among the quetiapine SR- and placebo-treated patients in the placebo-controlled studies is presented in Table 7.1.8.3.3.1 below. The most common abnormality leading to dropout was hypotension or orthostatic hypotension. No placebo patient dropped out due to a vital sign abnormality.

Table 7.1.8.3.3.1: Dropouts (n(%)) Due to Vital Sign Abnormalities Placebo-Controlled Studies		
Vital Sign Abnormality	**Quetiapine SR N=951**	**Placebo N=319**
Hypotension/Orthostatic hypotension	4 (0.4%)	0
Tachycardia/Increased heart rate	2 (0.2%)	0
Blood pressure increased	2 (0.2%)	0
Pyrexia	1 (0.1%)	0

7.1.8.4 Additional analyses and explorations

There are no other analyses which would impact on the safety profile of quetiapine SR.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

In the placebo-controlled trials, 12-lead ECG's were recorded at screening and at the end of treatment. For studies 132 and 133, a pre-treatment ECG was required within seven days prior to randomization.

There is no new preclinical information in this application.

ECG data from the placebo-controlled studies were transmitted to the same ECG laboratory (eResearch), where they were processed through a computer interpretation program and then reviewed by an ECG analyst, followed by a board-certified cardiologist.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Analyses of ECG data are based on the pool of the three placebo-controlled trials. This review encompassed evaluations of the incidence of potentially clinically significant ECG findings as well as dropouts due to ECG abnormalities.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Analyses of mean changes in ECG parameters are not well suited to detect occurrences of significant ECG findings and, therefore, are not included in this review.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.1.9.3.2.1 below depicts the percentages of quetiapine SR and placebo patients in the three placebo-controlled studies who experienced potentially clinically important (PCI) ECG parameter values at any time during treatment. Criteria for PCI measures are provided in the table. The QT interval was corrected using the Fridericia method.[12] Change values are from randomization to the time of measurement.

Table 7.1.9.3.2.1: Incidence of Potentially Clinically Important ECG Measurements Placebo-Controlled Studies

Measure (units)	PCI Criterion	Quetiapine SR			Placebo		
		N_R	N_{PCI}	$\%_{PCI}$	N_R	N_{PCI}	$\%_{PCI}$
Heart rate (bpm)	**>120**	781	6	0.8	253	0	0
	<50	769	2	0.3	250	5	2.0
	≥15 incr	782	226	28.9	253	35	13.8
	≥15 decr	782	44	5.6	253	41	16.2
PR (ms)	**≥210**	777	0	0	250	0	0
QRS interval (ms)	**≥120**	778	4	0.5	252	0	0
	≤50	782	0	0	253	0	0
QT interval (ms)	**≥500**	782	0	0	253	0	0
	≥60 incr	782	5	0.6	253	3	1.2
QTc (ms)	**≥450**	773	5	0.6	250	2	0.8
	≥60 incr	782	2	0.3	253	0	0

The only measure on which the proportion of drug patients with a PCI value was statistically significantly higher than the corresponding placebo proportion was an increase in heart rate of 15 bpm or greater (28.9% versus 13.8%, $p<0.0001$; alpha=0.10). This is consistent with the similar finding based on vital sign data discussed above. There was no evidence of a clear dose-response relationship between quetiapine SR dose and incidence of a substantial increase in heart rate: for the 400, 600, and 800mg dose groups, the frequency of this abnormality was 27%, 27%, and 34%, respectively. The mean change in heart rate from randomization to end of treatment, which is cited in the sponsor's proposed labeling, was +7.36 bpm for quetiapine SR and -0.65 bpm for placebo.

No patient in the placebo-controlled trials experienced a QTc value of 500 msec or greater during study treatment.[13]

[12] Since quetiapine does appear to be associated with an increase in heart rate, use of the Fridericia correction method, as opposed to the Bazett's formula, seems appropriate.
[13] Patient E0505033 in study 132 did have a QTc of 507 msec at the time of enrollment (prior to study drug treatment). This patient was discontinued from the trial due to failure to meet eligibility criteria.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Two patients are listed by the sponsor as having dropped out due to ECG abnormalities, both with increases in heart rate and both within the first week of study drug treatment: patient E0805008 in study 132 had received quetiapine SR 400 mg/day and patient E0007022 took quetiapine SR 600 mg/day. Both patients experienced other adverse events at about the same time and it is unclear to what extent the increase in heart rate contributed to the decision to discontinue study participation. No other patients were designated as dropping out due to an ECG abnormality.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations of ECG data were conducted.

7.1.10 Immunogenicity

No immunogenicity studies were performed.

7.1.11 Human Carcinogenicity

No carcinogenicity study data was submitted with this application.

7.1.12 Special Safety Studies

Four clinical pharmacology studies were performed to establish a starting dose of quetiapine SR (studies 87 and 98) and evaluate a dose escalation scheme for quetiapine SR (studies 109 and 145) for use in the subsequent safety and efficacy trials. The results are summarized below.

Studies 87 and 98 were conducted in patients with schizophrenia, schizoaffective disorder, and bipolar disorder. Study 109 was done in patients with schizophrenia, schizoaffective disorder, or disorganized schizophrenia whereas study 145 examined patients with schizophrenia or schizoaffective disorder.

Study 87 compared the safety and tolerability of four fixed doses of quetiapine SR (50, 100, 200, and 300mg) with quetiapine IR doses given according to approved labeling. No safety or tolerability issues were identified with the 300mg starting dose.

Study 98 was similarly designed and examined doses of quetiapine SR 400, 600, and 800mg. A starting dose of 400mg increased pulse rates up to 160 bpm and the study was prematurely terminated. This investigation suggested that starting doses of 400mg (and higher) may not be well tolerated.

Study 109 provided evidence of safety and good tolerability when quetiapine SR was started at 300mg, escalated to 600mg by day 5, and then escalated to 800mg by day 8. This dosing

regimen was compared to patients who received a fixed dose of 300 mg/day throughout the study. This dose escalation schedule was utilized in the Phase 3 study 41.

Study 145 compared the safety and tolerability of two different dose escalation schemes for use in the pivotal studies (studies 132 and 133) with patients who received a fixed dose of 300 mg/day. One escalation scheme allowed patients to reach a dose of 800mg by day 4 and the other allowed patients to reach a dose of 800mg by day 3. The results of this study supported the selection of the 3-day dose escalation scheme, which was used in studies 132 and 133.

Additionally, study 146 evaluated the feasibility of switching from quetiapine IR to quetiapine SR in adult outpatients with schizophrenia. This study was comprised of a 4-week run-in period followed by a 6-week, randomized, double-blind, double-dummy phase in which patients receiving a stable fixed dose of quetiapine IR (400, 600, or 800 mg/day) were randomized in a 1:2 ratio to continue treatment with quetiapine IR at the same dose (N=166) or be switched to the same total daily dose of quetiapine SR (N=330). In terms of efficacy, a slightly higher proportion of patients who switched to quetiapine SR discontinued due to lack of efficacy (2.1% versus 0.6%) or had an increase in PANSS total score of 20% or more (8.5% versus 6.6%) based on week 6 LOCF results in the modified intent-to-treat population. The fraction of patients meeting either criterion was 9.1% of the patients switched to the SR formulation and 7.2% of the patients continuing quetiapine IR. Also, comparison of the two groups in terms of total adverse event frequency, incidence of serious adverse events, adverse events leading to discontinuation, and occurrence of tachycardia, orthostatic hypotension, and somnolence revealed that switching from IR to an equal dose of SR was safe and well tolerated.

In addition, study 115 explored the safety and tolerability of quetiapine SR in elderly patients with Alzheimer's disease who had symptoms of psychosis and/or agitation. In this multicenter, randomized, double-blind, double-dummy investigation, patients were randomized in a 2:1 ratio to either quetiapine SR or quetiapine IR, respectively, for six weeks of treatment. On day 1, quetiapine SR was initiated at a dose of 50 mg/day and quetiapine IR at a dose of 25 mg/day. On day 2, quetiapine IR was increased to 50 mg/day administered on a twice daily basis. Both formulations were increased to 100 mg/day on day 4. From day 8 on, the dose was titrated to a maximum of 300 mg/day (or decreased down to 50 mg/day) based on tolerability and clinical response. A total of 100 patients were randomized, 68 to quetiapine SR and 32 to quetiapine IR. Both dosing regimens were safe and well tolerated in terms of the frequency and nature of adverse events.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No systematic studies of withdrawal effects were conducted. There were no reports of abuse of quetiapine SR in the conducted studies.

7.1.14 Human Reproduction and Pregnancy Data

There were no reported pregnancies with quetiapine SR.

7.1.15 Assessment of Effect on Growth

The effect of quetiapine SR on growth was not assessed in these trials, which were conducted almost entirely in adult patients.

7.1.16 Overdose Experience

There were no reports of quetiapine SR overdose in the original safety database (Phase 1-3 trials).

There was one report of accidental overdose due to illness relapse in the Four-Month Safety Update (patient E3802007 in study 147). This event was non-fatal and apparently not associated with any adverse events. The amount of drug ingested is unclear from the documentation provided.

7.1.17 Postmarketing Experience

Quetiapine SR has not been marketed in any country. Thus, there are no postmarketing data available at this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The quetiapine SR development program was comprised of 18 completed and three ongoing human studies:

• seven pharmacokinetic studies.
• five clinical pharmacology studies.
• four clinical safety and efficacy studies in patients with schizophrenia, including three placebo-controlled studies (studies 41, 132, and 133) and one active-controlled study (study 146).
• two other studies, specifically a safety/ tolerability study in patients with Alzheimer's disease (115) and a pharmacokinetic study in adolescents with schizoaffective disorder, which was prematurely terminated after enrolling one patient (study 116).

• three ongoing studies at the time of the original submission, namely a relapse prevention study in schizophrenia (study 4), a safety/tolerability study in healthy volunteers (study 13), and an open-label switching study in patients with schizophrenia (study 147).

These studies are listed by study type in Table 7.2.1.1.1 below.

Table 7.2.1.1.1: Listing of Human Studies by Study Type	
Study Type	**Study Numbers**
Pharmacokinetic Studies	1, 3, 36, 37, 86, 97, 118.
Clinical Pharmacology (PD) Studies	8, 87, 98, 109, 145.
Safety and Efficacy in Schizophrenia	41, 132, 133, 146.
Other Completed Studies	115, 116.
Ongoing Studies	4, 13, 147.

This program included over 2,400 patients with schizophrenia or other psychotic disorders, of whom more than 1,500 were treated with quetiapine SR.

Based on data provided in the table of studies, 155 subjects received quetiapine SR in pharmacokinetic studies, 225 received quetiapine SR in clinical pharmacology (pharmacodynamic) studies, and 69 in the two other completed studies.

In the four Phase 3 safety and efficacy studies in schizophrenic patients, a total of 1,282 patients received quetiapine SR and, of these, 951 were treated in one of the three placebo-controlled trials (studies 41, 132, and 133). An enumeration of patients by treatment group in the pool of the Phase 3 trials is displayed in Table 7.2.1.1.2 below.

Table 7.2.1.1.2: Enumeration of Enrolled Patients Phase 3 Studies				
Study	**Quetiapine SR**	**Quetiapine IR**	**Placebo**	**Total**
41	272	176	84	532
132	347	123	118	588
133	332	116	117	565
146	331	166	0	497
Total Phase 3	1282	581	319	2182
Total Phase 3 Placebo-Controlled14	951	415	319	1685

14 The safety population included all randomized patients who took study drug. One enrolled Quetiapine IR patient

See section 7.2.1.3 for an enumeration of quetiapine patients by fixed dose group.

The studies which were ongoing at the time of the original submission were complete at the time of the Four-Month Safety Update on 11-16-06 and are summarized below.

• Study 4 – a study of relapse prevention in patients with schizophrenia (N_{safety} = 327). Patients were switched from previous antipsychotic treatment to quetiapine SR, in the flexible daily dose range of 400 to 800 mg/day. Treatment continued during a stabilization period that preceded randomization. Patients had to be stable and minimally symptomatic for 16 weeks to be eligible for randomization to continued quetiapine SR or placebo. A total of 197 patients completed the stabilization phase and were randomized. Although randomized therapy was to continue for one year, an initial pre-planned interim analysis of the first 45 relapse cases showed that quetiapine SR significantly prolonged the time to relapse and the study was terminated.
• Study 13 – a randomized, double-blind, two-period crossover study to compare the safety and tolerability of a titration of quetiapine SR with placebo in healthy volunteers (N_{safety} = 68). The cross-over periods consisted of a seven-day treatment interval with quetiapine SR or placebo separated by a washout of at least six days. Placebo was given on day 1, then quetiapine SR (or matching placebo) was given in doses of 50mg (days 2 and 3), 150mg (days 4 and 5), and 300mg (days 6 and 7). Intolerability was determined by non-inferiority testing of a composite score from predefined safety variables, including orthostatic blood pressure changes, drowsiness, and syncope. This study is intended to support other indications, including major depression and generalized anxiety disorder.
• Study 147 – a 12-week, open-label, non-comparative study in patients with schizophrenia to evaluate the feasibility of switching any antipsychotic treatment to quetiapine SR (N_{safety} = 477). Treatment was initiated during a four day cross-titration phase where ongoing antipsychotic medication was phased out and quetiapine SR was phased in over three days. For the next 12 weeks, quetiapine SR was administered using flexible dosing in the range 400 to 800 mg/day. Response was measured as the proportion of patients at week 12 who had an improved clinical benefit based on an assessment of clinical efficacy combined with tolerability on the CGI-Clinical Benefit (CGI-CB) score. A total of 370 patients completed the study.

7.2.1.2 Demographics

Demographic characteristics of patients by treatment group in the placebo-controlled Phase 3 study pool are displayed in Table 7.2.1.2.1 below. The following differences across treatment groups are noted:

• a larger percentage of females in the quetiapine IR 400mg group compared to the other groups.
• a lower mean age in the quetiapine IR 400mg group.
• a smaller percentage of Blacks in the quetiapine IR 400mg group.

did not take the study drug and, thus, was excluded from the placebo-controlled safety population.

• a larger percentage of Blacks in the quetiapine IR 800mg group.
• a larger percentage of other races (all Oriental) in the quetiapine IR 400mg group.

Table 7.2.1.2.1: Demographic Characteristics Phase 3 Placebo-Controlled Studies

Treatment Group	Gender(%)		Age (yrs)		Race (%)		
	Male	Female	Mean	Range	White	Black	Other
Placebo	68%	32%	38	18-65	46%	32%	22%
SR 300mg	74%	26%	39	18-64	52%	36%	12%
SR 400mg	70%	30%	38	18-61	45%	32%	23%
SR 600mg	69%	31%	38	18-61	48%	34%	18%
SR 800mg	72%	28%	38	18-63	51%	30%	19%
Total SR	71%	29%	38	18-64	49%	32%	19%
IR 300mg	76%	24%	39	19-62	48%	39%	13%
IR 400mg	59%	41%	34	18-62	59%	6%	35%
IR 600mg	73%	27%	40	21-60	44%	37%	19%
IR 800mg	64%	36%	41	19-65	27%	62%	11%
Total IR	67%	33%	38	18-65	45%	35%	20%

No patients under the age of 18 or over the age of 65 took part in the placebo-controlled studies.

However, it should be noted that 68 patients with Alzheimer's disease in the age range 65 to 94 years (mean age 80.47 years) were treated with quetiapine SR in study 115, which is described in section 7.1.12 above.

7.2.1.3 Extent of exposure (dose/duration)

The duration of exposure by dose group during randomized treatment in the placebo-controlled studies is displayed in Table 7.2.1.3.1 below.

Table 7.2.1.3.1: Mean Duration of Exposure to Study Medication by Dose Group Phase 3 Placebo-Controlled Studies

Dose Group	N	Duration of Exposure (days)		
		≤28	>28 and ≤42	>42
Placebo	319	123	132	64
SR 300mg	91	51	36	4
SR 400mg	227	60	102	65
SR 600mg	310	103	136	71
SR 800mg	323	105	146	72
Total SR	951	319	420	212
IR 300mg	90	47	37	6

IR 400mg	123	23	59	41
IR 600mg	86	48	35	3
IR 800mg	115	48	48	19
Total IR	414	166	179	69

The total number of patient exposure years (PEY's) for each treatment is as follows:15

• Quetiapine SR = 82.9 patient-years.
• Quetiapine IR = 33.3 patient-years.
• Placebo = 26.7 patient-years.

Of the 82.9 PEY's with quetiapine SR, 5.8 were with 300mg, 21.5 with 400mg, 27.1 with 600mg, and 28.5 with 800mg.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were no other known studies conducted with quetiapine SR.

7.2.2.2 Postmarketing experience

Since quetiapine SR has not been marketed, there are no post-marketing data.

7.2.2.3 Literature

A worldwide literature search was requested from the sponsor subsequent to the filing meeting for this application. AstraZeneca responded on 10-17-06 via a formal submission.

Published literature from 8-1-05 through 7-31-06 was reviewed utilizing Planet (an internal AstraZeneca database), BIOSYS Previews, EMBASE, IPAB, PsycINFO, and Ovid MEDLINE(R). The search was designed to capture all relevant safety information pertaining to the use of the active ingredient, quetiapine.

The sponsor states that, in their opinion, the results of the search reflect the known safety profile for Seroquel IR and do not highlight any additional issue affecting the safety of Seroquel SR.

I performed a search of the literature on 3-12-07 using PubMed with the search string "quetiapine AND (sustained release OR SR)" with no limits on the search criteria. This

15 Patient-years = (N × mean duration in days)/365.

produced four published articles. I reviewed the abstract of each article and none revealed a safety problem associated with the use of any quetiapine agent.

7.2.3 Adequacy of Overall Clinical Experience

Given that this product is a new formulation of an already marketed product and that the AUC and Cmax of the SR and IR formulations are comparable, the overall clinical experience with quetiapine SR to date is judged to be adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was deemed necessary for this product.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing conducted in the development program for quetiapine SR is felt to be adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No major differences in the metabolism, clearance, or potential for interactions is expected for quetiapine SR versus the marketed IR formulation. Thus, this workup is not deemed necessary for the approval of this product.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation for potential adverse events is adequate in this case. The complete safety findings from the long-term relapse prevention trial, study 4, have been submitted to the Agency as a separate supplement for review and will shed some light on the safety profile of quetiapine SR with extended use. Therefore, no recommendations for further study are warranted at this time.

7.2.8 Assessment of Quality and Completeness of Data

The quality of the safety data was addressed in two formal audits conducted by Dr. Dubitsky: 1) examination of the accuracy and completeness of adverse event information in narrative summaries and case report tabulations relative to information contained in the corresponding Case Report Forms (CRF's) and 2) evaluation of the acceptability of the adverse coding from verbatim (investigator) terms to MedDRA preferred terms.

The CRF audit compared the adverse event information in CRF's, narratives, and case report tabulations (.xpt files) for about 5% of the 214 patients for whom CRF's were submitted with the original application. These 11 patients are listed in Table 7.2.7.1 below.

Table 7.2.7.1: Adverse Event Audit List of Patients Audited (Study/Center/Patient Number)	
041/26/0451	133/44/044034
041/28/0513	133/47/047004
132/503/0503007	146/1406/1406002
132/506/506009	146/2204/2204001
133/15/015001	115/33/003306
133/19/019015	

This audit revealed good consistency of adverse event information across these three sources of adverse event data.

The acceptability of the adverse event coding, which was performed by the sponsor, was assessed by comparing each verbatim term to the corresponding preferred term (and vice-versa) for the Phase 3 placebo-controlled studies (41, 132, and 133), utilizing the adverse event line listing (.xpt file) for each study. This audit did not reveal any significant deficiencies.

7.2.9 Additional Submissions, Including Safety Update

A Four-Month Safety Update Report was submitted by the sponsor on 11-16-06. This report contains data from three studies that were ongoing at the time of the original application submission.

These studies are now complete. Findings with respect to deaths, non-fatal serious adverse event, and dropouts due to adverse events have been incorporated into the appropriate parts of section 7.1 of this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The clinical review of the safety database for the Seroquel SR development program revealed no findings which were attributable to quetiapine treatment and inconsistent with the previously observed safety profile for Seroquel.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The primary source of safety data was the pool of the three Phase 3 placebo-controlled studies (41, 132, and 133). All three studies were six-week, randomized, double-blind, fixed dose comparisons of the safety and efficacy of quetiapine SR, quetiapine IR, and placebo in acutely ill patients with schizophrenia. There are some differences, however, between study 41, on the one hand, and studies 132 and 133, on the other:

1) study 41 used a slower rate of dose titration than studies 132 and 133 (for example, high dose patients were titrated to 800mg by day 8 in study 41 and by day 3 in studies 132 and 133).
2) quetiapine SR was dosed in the morning in study 41 and in the evening in the other two studies.
3) the lowest fixed dose in study 41 was 300 mg/day but 400 mg/day in the other studies.
4) hospitalization was required for the first 10 days in study 41 but was optional in the other studies.
5) patients with diabetes mellitus were permitted in study 41 but were specifically excluded in the other studies.
6) the procedure for measuring orthostatic blood pressure was different in study 41 (after 5 minutes of rest, then after 30 seconds or less of standing) versus studies 132 and 133 (after 10 minutes at rest, then 2 minutes of standing).

Thus, for orthostatic pulse and blood pressure data, analyses were based on the pool of only 132 and 133.

Otherwise, all three studies were pooled for safety analyses with the exception of deaths and other serious adverse events, which were examined across the all Phase 1, Phase 2, and Phase 3 studies. Note that safety data from the three studies that were ongoing at the time of the original application (studies 4, 13, and 147) were not included in that submission but were reported in the Four-Month Safety Update and are incorporated into the appropriate parts of section 7.1 of this review.

7.4.1.2 Combining data

Despite the above difference between study 41 and the other two studies, no formal weighting method was utilized by the sponsor in pooling data across the three Phase 3 studies. It would be difficult to formulate a rationale method for accomplishing this and, in most important respects, these studies are similar. Thus, I have no objection to the sponsor's pooling of unweighted data in this case.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

A possible dose-dependent relationship was observed for increased pulse rate in the placebo-controlled study pool: at the 400, 600, and 800mg fixed doses of quetiapine SR, the proportions of patients experiencing an increase in pulse rate of at least 15 bpm were 29%, 42%, and 45%, respectively. When heart rate data were derived from ECG recordings, however, this relationship was less clear, with frequencies of this abnormality observed in 27%, 27%, and 34% of these groups, respectively.

There was no evidence of a clear dose-dependent relationship in the incidence of any of the four common, drug-related adverse events (dry mouth, somnolence, dizziness, and dyspepsia), elevated triglyceride levels, or substantial weight increases.

7.4.2.2 Explorations for time dependency for adverse findings

In the absence of long-term, placebo-controlled data, an adequate assessment of the time-dependency for adverse events could not be undertaken.

7.4.2.3 Explorations for drug-demographic interactions

Two drug-demographic interactions were observed with respect to the four common, drug-related adverse experiences: 1) older patients were at an increased risk of dry mouth compared than younger patients and 2) females were at an increased risk of dizziness compared to males. See section 7.1.5.6.2 above for further details. The clinical significance of these findings is unknown.

7.4.2.4 Explorations for drug-disease interactions

Drug-disease interactions were not specifically studied in the quetiapine SR trials.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interaction studies were conducted.

7.4.3 Causality Determination

Causality of common adverse events in this safety database was judged based on a comparison with the corresponding placebo incidence: an incidence among drug-treated patients at least twice the placebo incidence is the generally accepted criterion for a causal relationship.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Study 132 was a fixed dose study of QTP SR that examined doses of 400, 600, and 800 mg/day versus placebo in the treatment of schizophrenia. All three dose groups produced a significant difference over placebo.

Patients were randomized to 400, 600, and 800 mg treatment groups. For all dose groups, dosing for QTP SR began at 300 mg/day for the first day of treatment. For the 600 and 800 mg treatment groups, dosage was increased to 600 mg/day at Day 2. For the 800 mg treatment group, dosage was increased to 800 mg/day at Day 3.

Based on drug/placebo comparisons, there was evidence of a significant treatment effect for the low dose ($p<0.05$), and results at the two higher doses had greater robustness ($p<0.001$), but were similar in magnitude of effect size [LS mean change from baseline of -24.8 (SE=2.5, 95% CI = -29.8 to -19.9), -30.9 (SE=2.5, 95% CI = -35.8 to -26.0), and -31.3 (SE=2.5, 95% CI= -36.1 to -26.4) for 400 mg, 600 mg, and 800 mg, respectively]. There is overlap of the 95% CI's among all three doses. Therefore, there appears to be no advantage of the higher doses (600 and 800 mg) over the lower dose (400 mg).

The sponsor wishes to include language in labeling regarding switching patients from QTP IR to QTP SR at the equivalent total daily dose. In support of this language, they submitted the results of study 146, an international, multicenter (74 centers in 14 countries [in Australia, Europe, Asia, U.S., Africa and Canada]), double-blind, randomized, parallel group, double-dummy study in outpatients with schizophrenia. This study consisted of a 4-week run-in period to ensure patients were clinically stable (CGI Severity of Illness ≤ 3 with no changes from enrollment to randomization) and on a stable dose of QTP IR for at least 4 weeks prior to randomization. Patients taking QTP IR 300 to 450 mg/d at enrollment received QTP IR 400 mg/d during the run-in period, patients taking QTP 475 to 650 mg/d received 600 mg/d and patients taking 675 to 800 mg/d received 800 mg/d during the run-in period. Eligible patients were randomized to 6 weeks of treatment with a fixed dose of either the same dose of QTP IR or the same total daily dose of QTP SR at a ratio of 1:2. The primary outcome variable was the proportion of patients who discontinued due to lack of efficacy or whose PANSS total score increased 20% or more from randomization at any visit. The hypothesis was that the proportion of patients in the IR/SR treatment sequence was lower than the proportion of patients in the IR/IR treatment sequence plus 6% (non-inferiority margin). A one-sided non-inferiority test with margin 6% resulted in a p-value of 0.0431, for which a p-value ≤ 0.025 indicates non-inferiority of SR versus IR. Thus, the results of study 146 do not provide evidence for switching patients from QTP IR to QTP SR at the equivalent total daily dose.

8.2 Drug-Drug Interactions

Per Greg Dubitsky, M.D., there were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

8.3 Special Populations

Please see Section 6.1.4.

8.4 Pediatrics

The FDA has granted a deferral for the requirement of submitting pediatric data in this NDA. The deferral for conducting pediatric studies in the SEROQUEL SR clinical development program was agreed to at the June 20, 2002 pre-NDA meeting[16] between the Division of Neuropharmacological Drug Products and AstraZeneca. The Division stated that deferral of pediatric schizophrenia studies for the CR form pending completion of work with the IR form remained acceptable, during a January 14, 2005 pre-sNDA meeting to discuss the SEROQUEL Bipolar Depression program.

On February 11, 2003, the Division issued a Pediatric Written Request for SEROQUEL Tablets (NDA 20-639) for the treatment of schizophrenia and bipolar mania. AstraZeneca states it is currently working to fulfill the Written Request through the conduct of an ongoing pediatric clinical development program. (b) (4)

(b) (4)

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacologic Drugs Advisory Committee.

[16] Please note that the information concerning this meeting is taken from the sponsor's submission, because there were no FDA meeting minutes in DFS and, per 3/28/06 emails from the project manager supervisor, Paul David, and project manager, Kimberly Updegraff, such minutes for this meeting are nonexistent.

8.6 Literature Review

The sponsor stated that overall conclusions regarding the safety of Seroquel SR were supported by the results of a worldwide literature search for Seroquel IR (immediate release) tablets reported in the Periodic Safety Report dated 19 September 2005, Section 7.3 Published Studies. They report that this literature search was recently repeated for the PSUR dated 20 September 2006.

The literature from 01 August 2005 through 31 July 2006 for SEROQUEL was reviewed utilizing Planet (an internal AstraZeneca database), BIOSYS Previews, EMBASE, IPAB, PsycINFO, and Ovid MEDLINE(R). The search was designed to capture all relevant safety information with the use of the active ingredient, quetiapine.

The sponsor stated that in their opinion, the results of the literature searches reflect the known safety profile for Seroquel IR and do not highlight any additional issue affecting the safety of Seroquel SR.

8.7 Postmarketing Risk Management Plan

There are no additional recommendations.

8.8 Other Relevant Materials

The Division of Medication Errors and Technical Support (DDMAC) found the sponsor's initially proposed proprietary name, Seroquel SR, acceptable from a promotional perspective (OSE Review 06-0022, dated 3/6/06).

The Division of Medication Errors and Technical Support (DMETS) found the sponsor's initially proposed proprietary name, Seroquel SR, concerning for a) potential for confusion between the proposed extended-release tablet and the existing immediate-release tablet and b) misrepresentation of a once-a-day product with the suffix "SR" (OSE consult 06-0022, dated 3/6/06). The Division concurred and requested submission of another proposed proprietary name for evaluation. The sponsor requested reconsideration of the proposed proprietary name, Seroquel SR, and submitted an alternate name, Seroquel XR.

The Division issued an Information Request Letter including comments and requests from the Study Endpoints and Label Development (SEALD) Team concerning the sponsor's proposed PLR labeling on 3/13/07, and the sponsor responded with revised labeling on 3/20/07.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor has provided evidence from one study (study 132) that supports the claim of short-term efficacy for the use of QTP SR in schizophrenia at doses of 400 mg, 600 mg, and 800 mg once daily. The primary outcome measure in this study was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment.

Dr. Greg Dubitsky's clinical review of the safety database for the Seroquel SR development program revealed no findings which were attributable to quetiapine treatment and inconsistent with the previously observed safety profile for Seroquel.

9.2 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this application be granted approvable status.

In addition, it is recommended that the following be conveyed to the sponsor in the approvable letter:

1. Please provide information on withdrawal of your product in other countries and submission of marketing authorization applications to foreign regulatory agencies.
2. For study 041, according to the text of your submission, this study was conducted at 49 sites in the U.S. (45) and Canada (4). However, inspection of the list of study investigators reveals 66 sites in the U.S. (60) and Canada (6). Eleven (11) of these sites (9 in the U.S. and 2 in Canada) had no enrollment, which brings the number of enrolling sites to 55. Please clarify.

Final approval is contingent on satisfactory responses to the concerns conveyed in the approvable letter, satisfactory statistical, CMC, Pharm/Tox, and Biopharm reviews, and mutual agreement on labeling (see section 9.4).

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

9.3.1 Risk Management Activity

There are no recommendations for risk management beyond those already in the sponsor's proposed labeling and in the undersigned reviewer's comments on the sponsor's proposed labeling. Please see Section 9.4 for further details.

9.3.2 Required Phase 4 Commitments

It is recommended that the sponsor be required to perform at least one adequate and well controlled clinical trial to examine long-term safety and efficacy.

9.3.3 Other Phase 4 Requests

There are no additional recommendations.

9.4 Labeling Review

The following comments are based on a review of the clinical sections of sponsor's proposed labeling as presented in their March 20, 2007 submission.

HIGHLIGHTS OF PRESCRIBING INFORMATION
The heading "**WARNING: MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA**" should be modified to state "**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**".

The bullets
- "Atypical antipsychotic drugs (b) (4) an increased risk of death (5.1)
- Causes of death are variable (5.1)
- Quetiapine is not approved for elderly patients with Dementia-Related Psychoses (5.1)"

should be modified to state
- "Risk of death in atypical antipsychotic-treated patients was 1.6 to 1.7 times that in placebo-treated patients. (5.1)
- SEROQUEL XR (quetiapine) is not approved for treatment of patients with Dementia-Related Psychoses. (5.1)"

Another box should be added to state
"**WARNING: SUICIDALITY IN CHILDREN AND ADOLESCENTS** *See full prescribing information for complete boxed warning.*
- Antidepressants increased the risk of suicidality in short-term studies in children and adolescents. (5.2)
- Observe closely for clinical worsening, suicidality, or unusual changes in behavior. (5.2)
- Advise families and caregivers of the need for close observation and communication with the prescriber. (5.2)
- SEROQUEL XR is not approved for use in pediatric patients. (5.2, 8.4)"

HIGHLIGHTS OF PRESCRIBING INFORMATION/Indications and Usage
This section should be modified to state "SEROQUEL XR is indicated for the treatment of schizophrenia. (1)"

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

9.5 Comments to Applicant

See section 9.2 of this review.

Michelle M. Chuen, M.D.
April 9, 2007

Gregory M. Dubitsky, M.D.
April 9, 2007

cc: NDA 22-047
HFD-130/Division File
HFD-130/MChuen
/GDubitsky
/NKhin
/MMathis
/TLaughren
/KUpdegraff

10 APPENDICES

10.1 Review of Individual Study Reports

Study 132[17]

Investigators/Sites
Forty one investigators conducted this study at 41 sites in Europe (6 in Bulgaria, 5 in Greece, 6 in Romania, and 5 in Russia), Africa (7 in South Africa), and Asia (4 in India, 5 in the Philippines, and 3 in Indonesia). Investigators and sites are listed in Appendix 10.3.1 in Section 10.3 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to demonstrate superior efficacy of sustained-release (SR) quetiapine fumarate (SEROQUEL, quetiapine) for the three doses, 400mg/day, 600mg/day and 800mg/day, compared with placebo in the treatment of patients with schizophrenia.

Patient Sample
Important inclusion criteria were:

- age 18 to 65 years, inclusive
- documented clinical diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for any of the following:
  Schizophrenia
  - catatonic
  - disorganized
  - paranoid
  - undifferentiated
- a score of at least 4 on one or more of the following PANSS items at randomization Day 1: P1 – delusions; P2 - conceptual disorganization; P3 - hallucinatory behavior; P6 - suspiciousness/persecution
- PANSS total score of at least 70 at enrollment and at randomization Day 1
- CGI Severity of Illness score of at least 4 (moderately ill) at randomization Day 1 and worsening of the patient's condition during the 3 weeks immediately preceding the randomization CGI assessment, as judged by the investigator.

The following were relevant exclusion criteria:

- meeting the criteria for any other DSM-IV Axis I diagnosis, concomitant organic mental disorder or mental retardation

[17] Note that important protocol changes are incorporated into my description of the protocol.

- substance abuse or dependence as defined by DSM-IV and not in full remission
- hospitalization for the treatment of schizophrenic symptoms for a period of more than 1 month immediately before randomization
- a history of non-compliance as judged by the investigator
- known lack of response to two or more antipsychotics with adequate doses given for at least 4 weeks or requirement for clozapine treatment for symptom control, or treatment with clozapine within 1 month of the randomization.
- administration of a depot antipsychotic injection within 1 depot dosing interval before randomization
- use of fluoxetine within 14 days prior to randomization or use of antipsychotic, mood stabilizer, antidepressant, anxiolytic, hypnotic, or other psychoactive drugs within 48 hours before randomization and throughout the treatment period (except medications specified in *Concomitant Medications* below).

Design
This was a 6-week, international, multicenter, double-blind, double-dummy, randomized, placebo-controlled study. After the enrollment visit and an enrollment period of up to 7 days patients were randomized to one of the five treatment arms (QTP SR 400 mg/day, QTP SR 600 mg/day, QTP SR 800 mg/day, QTP IR 400 mg/day, or placebo) on Day 1, followed by a titration period and a fixed dose period of treatment. At randomization, patients were out-patients, in-patients or day patients at a hospital.

The investigational product was administered orally twice daily (with or without food). Dose initiation in each dose group is described in the table below, extracted from the sponsor's submission.

Treatment arm	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6-42
SR 400 mg	300 mg	400 mg	400 mg	400 mg	400 mg	400 mg
SR 600 mg	300 mg	600 mg	600 mg	600 mg	600 mg	600 mg
SR 800mg	300 mg	600 mg	800 mg	800 mg	800 mg	800 mg
IR 400 mg	50 mg	100 mg	200 mg	300 mg	400 mg	400 mg
Placebo	P	P	P	P	P	P

SR Queatiapine sustained-release; IR Quetiapine immediate-release; P placebo.

Tablet counts were based on dosing. The dosing schedule for each dose was according to the table below, extracted from the sponsor's submission.

Arm		400 mg SR	600 mg SR	800 mg SR	400 mg IR	Placebo
Day 1	AM	1x 25 mg IRPLA	1x 25 mg IRPLA	1x 25 mg IRPLA	1x 25 mg IR	1x 25 mg IRPLA
	PM	1x 25 mg IRPLA 1x 300 mg SR	1x 25 mg IRPLA 1x 300 mg SR	1x 25 mg IRPLA 1x 300 mg SR	1x 25 mg IR 1x 300 mg SRPLA	1x 25 mg IRPLA 1x 300 mg SRPLA
Day 2	AM	2x 25 mg IRPLA	2x 25 mg IRPLA	2x 25 mg IRPLA	2x 25 mg IR	2x 25 mg IRPLA
	PM	2x 25 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA	2x 25 mg IRPLA 1x 400 mg SR 1x 200 mg SR	2x 25 mg IRPLA 1x 400 mg SR 1x 200 mg SR	2x 25 mg IR 1x 400 mg SRPLA 1x 200 mg SRPLA	2x 25 mg IRPLA 1x 400 mg SRPLA 1x 200 mg SRPLA
Day 3	AM	1x 100 mg IRPLA	1x 100 mg IRPLA	1x 100 mg IRPLA	1x 100 mg IR	1x 100 mg IRPLA
	PM	1x 100 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	1x 100 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	1x 100 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	1x 100 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	1x 100 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA
Day 4	AM	1x 100 mg IRPLA	1x 100 mg IRPLA	1x 100 mg IRPLA	1x 100 mg IR	1x 100 mg IRPLA
	PM	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	1x 200 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA
Day 5	AM	1x 200 mg IRPLA	1x 200 mg IRPLA	1x 200 mg IRPLA	1x 200 mg IR	1x 200 mg IRPLA
	PM	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	1x 200 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA
Day 6-42	AM	1x 200 mg IRPLA	1x 200 mg IRPLA	1x 200 mg IRPLA	1x 200 mg IR	1x 200 mg IRPLA
	PM	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	1x 200 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA

IR Quetiapine immediate-release. IRPLA Quetiapine immediate-release placebo. SR Quetiapine sustained-release. SRPLA Quetiapine sustained- release placebo.

Quetiapine and placebo tablets were packed in wallets. Wallets packed based upon patient specific treatment were packaged into patient-specific cartons. Each carton contained 5 wallets, enough to last through the whole study for that subject. Each wallet also contained tablets for an extra 3 days of treatment. The investigational product was dispensed to the patient on Day 1 (randomization), Day 7, Day 14, Day 21 and Day 28. If the patient was hospitalized during the study the investigational product was kept by the ward staff and dispensed to the patient on a daily basis.

If patients were discontinued prematurely, the Day 42 (final visit) assessments were performed at end of treatment. Unsolicited AE reports occurring up to 30 days after last dose of investigational product were recorded together with concomitant medications in appropriate sections of the pCRF.

Efficacy Assessments
The protocol-defined primary efficacy variable was the Positive and Negative Syndrome Scale (PANSS) total score. No key secondary variables were identified.

Efficacy Analysis
The modified intent-to-treat (MITT) patients were those who:

- were randomized
- were given study treatment classified to the treatment which they were randomized to

- had a baseline value and at least one post-baseline PANSS assessment

The primary outcome measure was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment at Day 42. This measure was analyzed using an analysis of covariance (ANCOVA) model which included the independent variables for treatment and center, and baseline PANSS as a covariate. Fixed effects in the model were treatment and baseline PANSS, whereas center was regarded as a random effect. Least square means and confidence intervals for each treatment group were generated. In addition, between-treatment differences were estimated through calculation of point estimates of differences between least square means and associated 2-sided 95% confidence intervals. To confirm the result of the primary analysis, an analysis with country instead of center as a random effect in the ANCOVA model was performed.

If a patient dropped out before the Day 42 assessment, the PANSS total score for the actual last study assessment of that patient (if post baseline) was moved forward using LOCF. The LOCF approach was used as the primary method for handling of missing data. An alternative analysis using Observed Cases (OC) data was also carried out. In addition, a repeated measures analysis was performed to confirm the result from the primary analysis. The model included baseline score as a covariate, treatment as a fixed effect, center as a random effect and scheduled visit as a repeated measures factor. The interaction between treatment and visit was included in order to obtain treatment differences at each visit. An unstructured covariance pattern model was applied to the repeated measurements.

The multiplicity problem concerning the false-positive error rate for the three comparisons with placebo in the primary analysis was handled by utilizing the Hommel procedure. This ensured that the probability of getting a "false" success in any of the 3 comparisons was at most 5%; i.e., α=0.05. Thus, the p-values obtained from the 3 pair wise comparisons were ordered as $P_{(1)} \leq P_{(2)} \leq P_{(3)}$. If $P_{(3)} \leq 0.05$ then all null hypotheses associated with $P_{(1)}$, $P_{(2)}$ and $P_{(3)}$ were rejected. Otherwise the following algorithm was applied to calculate the adjusted p-values:

(i) $P^{adj}_{(3)}=P_{(3)}$

(ii) $P^{adj}_{(2)}$=minimum of $P_{(3)}$ or $P_{(2)}*2$

(iii) $P^{adj}_{(1)}$=minimum of $P_{(3)}$ or $P_{(2)}*(3/2)$ or $P_{(1)}*3$

Reject all $P^{adj} \leq \alpha$. No correction for multiplicity was applied to the comparison of quetiapine IR and placebo.

Baseline Demographics
The table below displays the demographic characteristics of the MITT patient sample by treatment group. No patient under age 18 or over age 64 participated in this study. There were no major differences between the 4 treatment groups with respect to age, gender, or race.

TABLE 10.1.2 : STUDY 132[18] BASELINE DEMOGRAPHICS, MITT POPULATION								
Treatment (n)	**Age (yrs)**		**Sex (%)**		**Race (%)**			
	Mean	**Range**	**Male**	**Female**	**White**	**Black**	**Oriental**	**Other**
QTP SR 400 mg (111)	34.1	18-61	70	30	57	4	39	0
QTP SR 600 mg (111)	34.2	18-58	55	45	60	4	36	1
QTP SR 800 mg (117)	34.4	18-60	60	40	61	4	35	0
QTP IR 400 mg (119)	34.4	18-62	58	42	60	6	34	0
Placebo (115)	34.1	18-64	58	42	59	4	36	0

Baseline Severity of Illness
Treatment groups had no major differences with respect to mean baseline PANSS total score (mean scores of 95.8 in QTP SR 400 mg patients, 96.8 in QTP SR 600 mg patients, 97.3 in QTP SR 800 mg patients, 96.5 in QTP IR 400 mg patients, and 96.2 in placebo patients).

Patient Disposition
Five hundred eighty eight (588) patients were randomized in this study. Fifteen (15) of these patients had no valid baseline or post-baseline PANSS score. Thus, 573 patients comprised the ITT sample (111 QTP SR 400 mg patients, 111 QTP SR 600 mg patients, 117 QTP SR 800 mg patients, 119 QTP IR 400 mg patients, and 115 placebo patients).

The numbers of MITT patients in-study over time are displayed in Appendix 10.3.3 in Section 10.3. At Day 42, 74% (82/111) of QTP SR 400 mg patients, 82% (91/111) of QTP SR 600 mg patients, 77% (90/117) of QTP SR 800 mg patients, 76% (90/119) of QTP IR 400 mg patients and 66% (76/115) of placebo patients completed the study. Based on the safety population, overall dropout rates were lower in the QTP SR 600 mg group [27% (30/113) of QTP SR 400 mg patients, 19% (21/113) of QTP SR 600 mg patients, 26% (31/121) of QTP SR 800 mg patients, 22% (27/123) of QTP IR 400 mg patients, and 28% (33/118) of placebo patients]. Based on the safety population, dropout rates due to lack of efficacy were also lower in the QTP

[18] Figures may not add up to 100% due to rounding.

SR 600 mg group [12% (13/113) of QTP SR 400 mg patients, 6% (7/113) of QTP SR 600 mg patients, 10% (12/121) of QTP SR 800 mg patients, 9% (11/123) of QTP IR 400 mg patients, and 14% (17/118) of placebo patients].

Dosing Information
This was a fixed dose study.

Concomitant Medications
The table below, extracted from the sponsor's submission, details the washout periods for restricted medications and states prohibited therapies.

Use category	Type of medication	Timelines and instructions	Reason (if applicable)
Permitted	Investigational products (quetiapine/placebo)	From randomization Day 1, and during the treatment period.	Study medication
	Any previous, current or new medications for medical illnesses, not listed under restricted or prohibited medication sections below.	As needed based on Investigator's judgment and the patients medical needs.	
	Agents designed to prevent pregnancy: intrauterine device in place, oral contraceptives, dermal contraceptives, injectable or implantable hormonal agents.	From enrolment until the end of the treatment period.	To avoid pregnancy during the study.
Restricted	Anticholinergic medication used prior to entry in the study	Should be discontinued at least 48 hours before randomization on Day 1 Thereafter, anticholinergic medications may be used to treat emergent EPS adverse events but not prophylactically during the treatment period	Use of anticholinergic medication is a secondary variable under study.

Use category	Type of medication	Timelines and instructions	Reason (if applicable)
	- Benztropine mesylate (up to 6 mg/day orally) may be administered. If this is not locally available, the following may be used: - Trihexyphenidyl up to 6 mg/day or - Biperiden 6 mg/day or - Procyclidine up to 30 mg/day	Prophylactic use is not allowed during the treatment period.	To treat emerging EPS adverse events
	Lorazepam (or oxazepam when lorazepam is not available in a given country) treatment for agitation is restricted during the treatment period	Up to 6 mg/day (60 mg/day for oxazepam) allowed as treatment for agitation during the treatment period; should be discontinued by Day 6.	To treat symptoms of agitation
	Patients taking medication for sleep can continue to do so provided they are only taken at bedtime. If sleep medications are initiated after enrolment, the allowed medications are: - Zolpidem tartrate: maximum permitted dose is 10 mg/day. - Chloral hydrate: maximum permitted dose is 2 g/day - Zaleplon: maximum permitted dose is 20 mg/day. - Zopiclone: maximum permitted dose is 7.5mg/day.	Restricted from enrolment until the end of the treatment period.	
Prohibited	Quetiapine, as medication outside the study	From enrolment until the end of the treatment period.	Medication under study and to avoid confounding factors

Use category	Type of medication	Timelines and instructions	Reason (if applicable)
	All antipsychotic or psychoactive medications including benzodiazipines, anxiolytic, mood stabilizer, antidepressant, hypnotic and sedative medication except those listed above in "permitted" or "restricted".	From enrolment until the end of the treatment period. Must be discontinued at least 48 hours before randomization on Day 1, regardless of the indication for which they have been prescribed.	Exclusion criteria
	Fluoxetine	Prohibited from 14 days prior to randomization until the end of the treatment period.	
	Depot and long-lasting antipsychotics	Within 1 dosing interval prior to randomization on Day 1and during the treatment period	Exclusion criteria
	All contraindicated medications, as detailed in country specific Prescribing Information for quetiapine	From enrolment until the end of the treatment period.	Patient safety
	Drugs that induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes; -*inducers:* e.g. phenytoin, carbamazepine, pentobarbital, rifampin, rifabutin, glucocorticoids, thioridazine and St John's wort and - - *inhibitors:* e.g. ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, fluvoxamine, nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir	Within 2 weeks prior to randomzation and during the treatment period	Exclusion criteria

With respect to the percentages of MITT population patients using various concomitant medications during the study, there were no major differences between treatment groups (47% in QTP SR 400 mg patients, 41% in QTP SR 600 mg patients, 43% in QTP SR 800 mg patients, 47% in QTP IR 400 mg patients, and 44% in placebo patients), and the most frequently used were lorazepam and zolpidem. Based on the safety population, there were 4/113 (4%) patients in the QTP SR 400 mg group, 7/113 (6%) patients in the QTP SR 600 mg group, 6/121 (5%) patients in the QTP SR 800 mg group, 6/123 (5%) patients in the QTP IR 400 mg group, and

5/118 (4%) patients in the placebo identified as protocol violators because of prohibited medication use.

Efficacy Results
Efficacy data displays may be found in the Appendices 10.3.2 to 10.3.5 in Section 10.3.

For the PANSS mean change from baseline analysis, the differences were statistically significant in favor of QTP SR in the LOCF analysis. The OC analysis was consistent with the LOCF analysis.

Per 9/6/06 emails from statistical reviewer, Yeh-Fong Chen, Ph.D., this study's efficacy results did not lose statistical significance with exclusion of any specific center.

Conclusions
The results of Study 132 provide evidence of the efficacy of QTP SR at doses of 400 mg, 600 mg, and 800 mg once daily in the treatment of schizophrenia versus placebo over 42 days of treatment.

Study 133

Because this study was a failed efficacy study, its efficacy results will not be described in detail.

Investigators/Sites
Forty four (44) investigators conducted this study at 44 sites in the U.S. Investigators and sites are listed in Appendix 10.3.6 in Section 10.3 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to demonstrate superior efficacy of sustained-release (SR) quetiapine fumarate (SEROQUEL, quetiapine) for the three doses, 400mg/day, 600mg/day and 800mg/day, compared with placebo in the treatment of patients with schizophrenia.

Patient Sample
Important inclusion criteria were:

- age 18 to 65 years, inclusive
- documented clinical diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for any of the following:
  Schizophrenia
  - catatonic
  - disorganized
  - paranoid
  - undifferentiated

- a score of at least 4 on one or more of the following PANSS items at randomization Day 1: P1 – delusions; P2 - conceptual disorganization; P3 - hallucinatory behavior; P6 - suspiciousness/persecution
- PANSS total score of at least 70 at enrollment and at randomization Day 1
- CGI Severity of Illness score of at least 4 (moderately ill) at randomization Day 1 and worsening of the patient's condition during the 3 weeks immediately preceding the randomization CGI assessment, as judged by the investigator.

The following were relevant exclusion criteria:

- meeting the criteria for any other DSM-IV Axis I diagnosis, concomitant organic mental disorder or mental retardation
- substance abuse or dependence as defined by DSM-IV and not in full remission
- hospitalization for the treatment of schizophrenic symptoms for a period of more than 1 month immediately before randomization
- a history of non-compliance as judged by the investigator
- known lack of response to two or more antipsychotics with adequate doses given for at least 4 weeks or requirement for clozapine treatment for symptom control, or treatment with clozapine within 1 month of the randomization.
- administration of a depot antipsychotic injection within 1 depot dosing interval before randomization
- use of fluoxetine within 14 days prior to randomization or use of antipsychotic, mood stabilizer, antidepressant, anxiolytic, hypnotic, or other psychoactive drugs within 48 hours before randomization and throughout the treatment period (except medications specified in *Concomitant Medications* below).

Design

This was a 6-week, multicenter, double-blind, double-dummy, randomized, placebo-controlled study. After the enrollment visit and an enrollment period of up to 7 days patients were randomized to one of the five treatment arms (QTP SR 400 mg/day, QTP SR 600 mg/day, QTP SR 800 mg/day, QTP IR 800 mg/day, or placebo) on Day 1, followed by a titration period and a fixed dose period of treatment. At randomization, patients were out-patients, in-patients or day patients at a hospital.

The investigational product was administered orally twice daily (with or without food). Dose initiation in each dose group is described in the table below, extracted from the sponsor's submission.

Treatment group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7-42
QTP SR 400 mg	300 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
QTP SR 600 mg	300 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg
QTP SR 800 mg	300 mg	600 mg	800 mg	800 mg	800 mg	800 mg	800 mg
QTP IR 800 mg	50 mg	100 mg	200 mg	300 mg	400 mg	600 mg	800 mg
Placebo	P	P	P	P	P	P	P

IR immediate-release. QTP quetiapine. SR sustained-release

Tablet counts were based on dosing. The dosing schedule for each dose was according to the table below, extracted from the sponsor's submission.

Gp		Quetiapine SR 400 mg/day	Quetiapine SR 600 mg/day	Quetiapine SR 800 mg/day	Quetiapine IR 800 mg/day	Placebo
Day 1	AM	1x 25 mg IRPLA	1x 25 mg IRPLA	1x 25 mg IRPLA	1x 25 mg IR	1x 25 mg IRPLA
	PM	1x 25 mg IRPLA 1x 300 mg SR	1x 25 mg IRPLA 1x 300 mg SR	1x 25 mg IRPLA 1x 300 mg SR	1x 25 mg IR 1x 300 mg SRPLA	1x 25 mg IRPLA 1x 300 mg SRPLA
Day 2	AM	2x 25 mg IRPLA	2x 25 mg IRPLA	2x 25 mg IRPLA	2x 25 mg IR	2x 25 mg IRPLA
	PM	2x 25 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA	2x 25 mg IRPLA 1x 400 mg SR 1x 200 mg SR	2x 25 mg IRPLA 1x 400 mg SR 1x 200 mg SR	2x 25 mg IR 1x 400 mg SRPLA 1x 200 mg SRPLA	2x 25 mg IRPLA 1x 400 mg SRPLA 1x 200 mg SRPLA
Day 3	AM	1x 100 mg IRPLA	1x 100 mg IRPLA	1x 100 mg IRPLA	1x 100 mg IR	1x 100 mg IRPLA
	PM	1x 100 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	1x 100 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	1x 100 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	1x 100 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	1x 100 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA
Day 4	AM	1x 100 mg IRPLA	1x 100 mg IRPLA	1x 100 mg IRPLA	1x 100 mg IR	1x 100 mg IRPLA
	PM	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	1x 200 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA
Day 5	AM	1x 200 mg IRPLA	1x 200 mg IRPLA	1x 200 mg IRPLA	1x 200 mg IR	1x 200 mg IRPLA
	PM	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	1x 200 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	1x 200 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA
Day 6	AM	1x 100 mg IRPLA 1x 200 mg IRPLA	1x 100 mg IRPLA 1x 200 mg IRPLA	1x 100 mg IRPLA 1x 200 mg IRPLA	1x 100 mg IR 1x 200 mg IR	1x 100 mg IRPLA 1x 200 mg IRPLA
	PM	1x 100 mg IRPLA 1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	1x 100 mg IRPLA 1x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	1x 100 mg IRPLA 1x 200 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	1x 100 mg IR 1x 200 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	1x 100 mg IRPLA 1x 200 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA
Day 7-42	AM	2x 200 mg IRPLA	2x 200 mg IRPLA	2x 200 mg IRPLA	2x 200 mg IR	2x 200 mg IRPLA
	PM	2x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SRPLA 1x 400 mg SRPLA	2x 200 mg IRPLA 1x 400 mg SR 1x 200 mg SR 1x 400 mg SRPLA	2x 200 mg IRPLA 2x 400 mg SR 1x 200 mg SRPLA	2x 200 mg IR 2x 400 mg SRPLA 1x 200 mg SRPLA	2x 200 mg IRPLA 2x 400 mg SRPLA 1x 200 mg SRPLA

Gp group. IR immediate-release. IRPLA immediate-release placebo. SR sustained-release. SRPLA Quetiapine sustained-release placebo.

Quetiapine and placebo tables were packed in bottles. Bottles packed based upon patient-specific treatment were packaged into patient-specific cartons. The number of bottles per carton

was based on the visit structure. Each carton contained three extra days of dosing. The investigational product was dispensed to the patient on Day 1 (randomization), Day 7, Day 14, Day 21 and Day 28. If the patient was hospitalized during the study the investigational product was kept by the ward staff and dispensed to the patient on a daily basis.

Efficacy Assessments
The protocol-defined primary efficacy variable was the Positive and Negative Syndrome Scale (PANSS) total score. No key secondary variables were identified.

Efficacy Analysis
The modified intent-to-treat (MITT) patients were those who:

- were randomized
- were given study treatment classified to the treatment which they were randomized to
- had a baseline value and at least one post-baseline PANSS assessment

The primary outcome measure was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment at Day 42. This measure was analyzed using an analysis of covariance (ANCOVA) model which included the independent variables for treatment and center, and baseline PANSS as a covariate. Fixed effects in the model were treatment and baseline PANSS, whereas center was regarded as a random effect. Least square means and confidence intervals for each treatment group were generated. In addition, between-treatment differences were estimated through calculation of point estimates of differences between least square means and associated 2-sided 95% confidence intervals.

Missing data resulting from patient withdrawals were imputed using an LOCF approach. Patients with post baseline data had their last study assessment carried forward as the final assessment for analyses.

The multiplicity problem concerning the false-positive error rate for the three comparisons with placebo in the primary analysis was handled by utilizing the Hommel procedure. This ensured that the probability of getting a “false" success in any of the 3 comparisons was at most 5%; i.e., α=0.05. Thus, the p-values obtained from the 3 pair wise comparisons were ordered as $P_{(1)} \leq P_{(2)} \leq P_{(3)}$. If $P_{(3)} \leq 0.05$ then all null hypotheses associated with $P_{(1)}$, $P_{(2)}$ and $P_{(3)}$ were rejected. Otherwise the following algorithm was applied to calculate the adjusted p-values:

(iv) $P^{adj}_{(3)}=P_{(3)}$

(v) $P^{adj}_{(2)}$=minimum of $P_{(3)}$ or $P_{(2)}*2$

(vi) $P^{adj}_{(1)}$=minimum of $P_{(3)}$ or $P_{(2)}*(3/2)$ or $P_{(1)}*3$

Reject all $P^{adj} \leq \alpha$. No correction for multiplicity was applied to the comparison of quetiapine IR and placebo.

Efficacy Results
Efficacy data displays may be found in the Appendix 10.3.7 in Section 10.3.

For the PANSS mean change from baseline analysis, the differences were not statistically significant.

Conclusions
The results of Study 133 do not provide adequate evidence of the efficacy of QTP SR in the treatment of schizophrenia versus placebo over 42 days of treatment.

Study 041

Because this study was a failed efficacy study, it will not be described in detail.

Investigators/Sites
According to the text of the sponsor's submission, this study was conducted at 49 sites in the U.S. (45) and Canada (4). However, inspection of the list of study investigators reveals 66 sites in the U.S. (60) and Canada (6). Eleven (11) of these sites (9 in the U.S. and 2 in Canada) had no enrollment, which brings the number of enrolling sites to 55. Investigators and sites are listed in Appendix 10.3.8 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to demonstrate superior efficacy of sustained-release (SR) quetiapine fumarate (SEROQUEL, quetiapine) tablets compared to placebo in the treatment of patients with schizophrenia.

Patient Sample
Important inclusion criteria were:

- age 18 to 65 years, inclusive
- documented clinical diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for any of the following:
  Schizophrenia
  - catatonic
  - disorganized
  - paranoid
  - undifferentiated
- a score of at least 4 on one or more of the following PANSS items at randomization Day 1: P1 – delusions; P2 - conceptual disorganization; P3 - hallucinatory behavior; P6 - suspiciousness/persecution
- PANSS total score of at least 60 at both screening and baseline (Day 1)

- CGI Severity of Illness score of at least 4 (moderately ill) at baseline (Day 1) and worsening of the patient's condition during the 3 weeks immediately preceding the randomization CGI assessment.

The following were relevant exclusion criteria:

- meeting the criteria for any other DSM-IV Axis I diagnosis, such as substance abuse or dependence not in full remission, or mental retardation
- hospitalization for the treatment of schizophrenic symptoms for a period of more than 1 month immediately before the baseline visit (Day 1)
- risk of non-compliance
- known lack of response to clozapine treatment, known requirement for clozapine treatment for symptom control, treatment with clozapine within 1 month of the randomization, or, in the opinion of the investigator, lack of response to antipsychotic medications
- administration of a depot antipsychotic injection within 1 depot dosing interval before randomization
- use of antipsychotic, mood stabilizer, antidepressant, anxiolytic, hypnotic, or other psychoactive drugs within 48 hours before randomization and throughout the treatment period (except medications specified in *Concomitant Medications* below).

Design

This was a 6-week, multicenter, double-blind, double-dummy, randomized, placebo-controlled study. After the enrollment visit and an enrollment period of up to 7 days patients were randomized to one of the six treatment arms (QTP SR 300 mg/day, QTP SR 600 mg/day, QTP SR 800 mg/day, QTP IR 300 mg/day, QTP IR 600 mg/day, or placebo) on Day 1, followed by a titration period and a fixed dose period of treatment. Patients who were screened as outpatients were hospitalized when enrolled. Patients could be discharged from the hospital on Day 10 at the investigator's discretion.

The investigational product was administered orally twice daily (with or without food). Placebo tablets were combined with quetiapine tablets to ensure that the tablets given to patients in all treatment groups for a given dose were identical in number and appearance. The tablets were packaged in blister cards designed so that patients assigned to treatment with quetiapine SR took active tablets in the morning and placebo only in the evening, while patients assigned to treatment with quetiapine IR took active tablets in the morning and in the evening. Dose initiation in each dose group is described in the tables below, extracted from the sponsor's submission.

Dose-escalation schemes for sustained-release quetiapine

Target dose	Total daily quetiapine dose (mg)		
	Days 1 through 4	Days 5 through 7	Days 8 through 42
300 mg	300	300	300
600 mg	300	600	600
800 mg	300	600	800

Dose-escalation schemes for immediate-release quetiapine

Target dose	Total daily quetiapine dose (mg)					
	Day 1	Day 2	Day 3	Day 4	Day 5	Days 6 through 42
300 mg	50	100	200	300	300	300
600 mg	50	100	200	300	400	600

Efficacy Assessments
The protocol-defined primary efficacy variable was the Positive and Negative Syndrome Scale (PANSS) total score. No key secondary variables were identified.

Efficacy Analysis
The modified intent-to-treat (MITT) patients were those who:

- took study treatment
- had a PANSS assessment before taking study treatment (baseline)
- had at least 1 PANSS assessment after taking study treatment

The primary outcome measure was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment at Day 42. This measure was tested for treatment effect using an ANCOVA model that included terms for center, treatment, and baseline score. All pairwise differences between least-squares means for the quetiapine treatment groups and the placebo treatment group were calculated, and 95% confidence intervals for these differences were constructed. The p-values from the pairwise comparisons of the 3 quetiapine SR treatment groups with the placebo group were rank ordered, and the Hochberg (1988) method was used to adjust for multiplicity. The p-values from the pairwise comparisons of the 2 quetiapine IR dose groups with the placebo group were not adjusted for multiplicity.

All statistical analyses used the last-observation-carried-forward (LOCF) value for patients who withdrew early or who had missing data.

Efficacy Results
Efficacy data displays may be found in the Appendices 10.3.9 in Section 10.3.

For the PANSS mean change from baseline analysis, the differences were not statistically significant.

Conclusions
The results of Study 041 provide evidence of the efficacy of QTP SR at a dose of 600 mg once daily in the treatment of schizophrenia versus placebo over 42 days of treatment. They do not provide evidence of the efficacy of QTP SR at doses of 400 mg and 800 mg once daily.

10.2 Line-by-Line Labeling Review

See section 9.4 for a discussion of the clinical changes to labeling based on this NDA.

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APPENDIX 10.3.2: RESULTS OF PRIMARY VARIABLE PANSS: CHANGE FROM BASELINE, ALL TIME POINTS, LOCF ANALYSIS, MITT POPULATION FOR STUDY 132

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
Day 7					
n	115	111	111	116	119
Baseline: mean (SD)[a]	96.2 (13.3)	95.8 (13.9)	96.8 (14.1)	97.4 (14.8)	96.5 (16.0)
Day 7 mean (SD)	87.1 (18.1)	86.3 (17.4)	89.2 (17.1)	86.1 (18.6)	88.4 (18.7)
Change from baseline					
LS mean (SE)	-9.2 (1.3)	-9.5 (1.3)	-7.8 (1.3)	-11.0 (1.3)	-8.1 (1.3)
95% CI	-11.7, -6.7	-12.1, -6.9	-10.4, -5.2	-13.6, -8.5	-10.6, -5.6
Difference between active therapy and placebo					
Estimated diff (SE)		-0.3 (1.6)	1.4 (1.6)	-1.8 (1.6)	1.1 (1.5)
95% CI		-3.4, 2.8	-1.7, 4.5	-4.9, 1.3	-1.9, 4.2
Day 14					
n	115	111	111	117	119
Baseline: mean (SD)[a]	96.2 (13.3)	95.8 (13.9)	96.8 (14.1)	97.3 (14.7)	96.5 (16.0)
Day 14 mean (SD)	81.9 (20.2)	81.2 (21.1)	81.8 (19.3)	78.8 (21.1)	81.3 (21.5)
Change from baseline					
LS mean (SE)	-14.9 (1.7)	-15.2 (1.8)	-15.8 (1.8)	-18.4 (1.7)	-15.6 (1.7)
95% CI	-18.3, -11.5	-18.7, -11.6	-19.3, -12.3	-21.9, -15.0	-19.0, -12.2
Difference between active therapy and placebo					
Estimated diff (SE)		-0.2 (2.1)	-0.9 (2.1)	-3.5 (2.0)	-0.7 (2.0)
95% CI		-4.3, 3.8	-5.0, 3.1	-7.5, 0.5	-4.7, 3.3
Day 21					
n	115	111	111	117	119
Baseline: mean (SD)[a]	96.2 (13.3)	95.8 (13.9)	96.8 (14.1)	97.3 (14.7)	96.5 (16.0)
Day 21 mean (SD)	78.1 (21.5)	76.0 (21.5)	76.4 (18.8)	73.6 (21.6)	76.6 (23.7)
Change from baseline					
LS mean (SE)	-18.8 (2.0)	-20.4 (2.0)	-21.3 (2.0)	-23.5 (2.0)	-20.2 (1.9)
95% CI	-22.7, -14.9	-24.4, -16.4	-25.2, -17.3	-27.4, -19.6	-24.0, -16.3
Difference between active therapy and placebo					
Estimated diff (SE)		-1.6 (2.3)	-2.5 (2.3)	-4.7 (2.3)	-1.4 (2.2)
95% CI		-6.1, 2.8	-7.0, 2.0	-9.1, -0.3	-5.7, 3.0

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
Day 28					
n	115	111	111	117	119
Baseline: mean (SD)[a]	96.2 (13.3)	95.8 (13.9)	96.8 (14.1)	97.3 (14.7)	96.5 (16.0)
Day 28 mean (SD)	78.1 (23.1)	73.6 (22.4)	70.8 (20.0)	69.8 (23.4)	74.1 (24.4)
Change from baseline					
LS mean (SE)	-18.8 (2.2)	-22.7 (2.2)	-26.7 (2.2)	-27.3 (2.2)	-22.5 (2.1)
95% CI	-23.0, -14.5	-27.0, -18.3	-31.1, -22.4	-31.6, -23.1	-26.7, -18.3
Difference between active therapy and placebo					
Estimated diff (SE)		-3.9 (2.5)	-8.0 (2.5)	-8.6 (2.5)	-3.8 (2.5)
95% CI		-8.9, 1.0	-12.9, -3.0	-13.5, -3.7	-8.6, 1.1
Day 42					
n	115	111	111	117	119
Baseline: mean (SD)[a]	96.2 (13.3)	95.8 (13.9)	96.8 (14.1)	97.3 (14.7)	96.5 (16.0)
Day 42 mean (SD)	78.2 (25.4)	71.6 (24.1)	66.9 (20.4)	66.0 (24.0)	70.2 (26.3)
Change from baseline					
LS mean (SE)	-18.8 (2.5)	-24.8 (2.5)	-30.9 (2.5)	-31.3 (2.5)	-26.6 (2.4)
95% CI	-23.6, -13.9	-29.8, -19.9	-35.8, -26.0	-36.1, -26.4	-31.4, -21.7
Difference between active therapy and placebo					
Estimated diff (SE)		-6.1 (2.8)	-12.1 (2.8)	-12.5 (2.8)	-7.8 (2.7)
95% CI		-11.5, -0.6	-17.6, -6.7	-17.9, -7.1	-13.1, -2.4

[a] The assessment made at randomization was considered baseline.
CI Confidence interval. IR Immediate-release. LOCF Last observation carried forward. LS Least squares. MITT Modified intention-to-treat. N Number of patients in treatment group. n Number of patients. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SE Standard error. SR Sustained-release.
Note: Analysis using analysis of covariance (ANCOVA) with the baseline score as covariate, treatment as fixed effect and center as random effect. Only patients with assessment at baseline are included.
Study:D1444C00132, Source document: ETC_PANSS_TOT_CHA22.SAS. Generated: 11:28:27 19May2006 DB version prod: 27.

APPENDIX 10.3.3: RESULTS OF PRIMARY VARIABLE PANSS: CHANGE FROM BASELINE, ALL TIME POINTS, OBSERVED-CASES ANALYSIS, MITT POPULATION FOR STUDY 132

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
Day 7					
n	114	110	109	114	117
BL mean (SD)	96.0 (13.1)	95.9 (13.9)	96.8 (14.3)	97.4 (14.8)	96.7 (16.0)
Day 7 mean (SD)	87.0 (18.2)	86.3 (17.4)	88.8 (16.9)	85.9 (18.5)	87.9 (18.4)
Change from BL					
LS mean (SE)	-9.0 (1.3)	-9.6 (1.3)	-8.2 (1.3)	-11.3 (1.3)	-8.7 (1.3)
95% CI	-11.5, -6.5	-12.1, -7.0	-10.7, -5.6	-13.8, -8.8	-11.2, -6.2
vs placebo					
Estimated diff (SE)		-0.6 (1.5)	0.9 (1.5)	-2.3 (1.5)	0.3 (1.5)
95% CI		-3.6, 2.5	-2.2, 3.9	-5.3, 0.7	-2.7, 3.3
Day 14					
n	114	105	106	106	111
BL mean (SD)	96.2 (13.3)	96.1 (13.5)	96.9 (14.3)	96.7 (14.4)	96.1 (16.3)
Day 14 mean (SD)	81.6 (20.0)	80.2 (20.7)	81.1 (19.3)	76.0 (19.2)	79.7 (20.9)
Change from BL					
LS mean (SE)	-15.3 (1.7)	-16.3 (1.8)	-16.5 (1.8)	-20.9 (1.8)	-16.9 (1.7)
95% CI	-18.7, -12.0	-19.7, -12.8	-20.0, -13.0	-24.4, -17.4	-20.3, -13.5
vs placebo					
Estimated diff (SE)		-0.9 (2.0)	-1.2 (2.0)	-5.6 (2.0)	-1.6 (2.0)
95% CI		-4.9, 3.1	-5.2, 2.8	-9.6, -1.6	-5.5, 2.4
Day 21					
n	104	96	102	103	105
BL mean (SD)	96.9 (13.2)	95.6 (13.3)	97.2 (14.5)	96.9 (14.6)	96.2 (16.4)
Day 21 mean (SD)	76.2 (20.4)	72.5 (19.7)	75.2 (18.3)	69.6 (18.5)	73.3 (21.5)
Change from BL					
LS mean (SE)	-21.3 (1.9)	-23.9 (1.9)	-22.9 (1.9)	-27.3 (1.9)	-23.3 (1.9)
95% CI	-25.0, -17.6	-27.7, -20.1	-26.6, -19.1	-31.1, -23.6	-27.0, -19.7
vs placebo					
Estimated diff (SE)		-2.6 (2.1)	-1.5 (2.1)	-6.0 (2.1)	-2.0 (2.1)
95% CI		-6.8, 1.6	-5.7, 2.6	-10.2, -1.8	-6.1, 2.1
Day 28					
n	95	88	99	96	100

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
BL mean (SD)	96.5 (13.0)	96.3 (13.5)	97.7 (14.3)	97.3 (14.5)	96.3 (16.8)
Day 28 mean (SD)	75.0 (22.6)	69.6 (20.8)	69.2 (19.3)	65.1 (20.0)	69.0 (21.0)
Change from BL					
LS mean (SE)	-22.1 (2.1)	-27.1 (2.2)	-29.0 (2.1)	-32.1 (2.1)	-27.3 (2.1)
95% CI	-26.3, -17.9	-31.4, -22.8	-33.1, -24.8	-36.3, -27.9	-31.4, -23.2
vs placebo					
Estimated diff (SE)		-5.0 (2.5)	-6.8 (2.4)	-10.0 (2.4)	-5.2 (2.4)
95% CI		-9.8, -0.1	-11.6, -2.1	-14.8, -5.2	-9.9, -0.5
Day 42					
n	76	82	91	90	90
BL mean (SD)	97.2 (13.2)	96.0 (13.8)	97.6 (14.1)	96.9 (14.7)	96.2 (16.7)
Day 42 mean (SD)	73.6 (26.1)	65.5 (21.8)	63.3 (18.0)	59.4 (18.6)	63.5 (21.1)
Change from BL					
LS mean (SE)	-23.1 (2.5)	-31.1 (2.5)	-35.1 (2.3)	-37.7 (2.4)	-33.1 (2.4)
95% CI	-28.0, -18.1	-36.0, -26.3	-39.7, -30.4	-42.4, -33.0	-37.7, -28.4
vs placebo					
Estimated diff (SE)		-8.1 (2.9)	-12.0 (2.9)	-14.6 (2.9)	-10.0 (2.8)
95% CI		-13.8, -2.4	-17.6, -6.4	-20.3, -9.0	-15.6, -4.4

CI Confidence interval. OC Observed cases. LS Least squares. MITT Modified intention-to-treat. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SR Sustained-release. BL Baseline. N Number of Patients in treatment group. N Number of patients. SE Standard Error.
Note: Analysis using of Covariance (ANCOVA) with the baseline score as covariate, treatment as fixed effect and center as random effect only Patients with assessment at baseline are included.
Study:D1444C00132, Source document: ETC_PANSS_TOT_CHA_OC131.SAS. Generated: 11:28:40 19May2006 DB version prod: 27.

APPENDIX 10.3.4: PANSS TOTAL SCORE, CHANGE FROM BASELINE AT DAY 42 FOR STUDY 132 (LOCF, MITT POPULATION)

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
n	115	111	111	117	119
Baseline: mean (SD)[a]	96.2 (13.3)	95.8 (13.9)	96.8 (14.1)	97.3 (14.7)	96.5 (16.0)
Day 42: mean (SD)	78.2 (25.4)	71.6 (24.1)	66.9 (20.4)	66.0 (24.0)	70.2 (26.3)
Change from baseline					
LS mean (SE)	-18.8 (2.5)	-24.8 (2.5)	-30.9 (2.5)	-31.3 (2.5)	-26.6 (2.4)
95% CI	-23.6, -13.9	-29.8, -19.9	-35.8, -26.0	-36.1, -26.4	-31.4, -21.7
Difference between active therapy and placebo					
Estimated difference (SE)		-6.1 (2.8)	-12.1 (2.8)	-12.5 (2.8)	-7.8 (2.7)
95% CI[b]		-11.5, -0.6	-17.6, -6.7	-17.9, -7.1	-13.1, -2.4
p-value (unadjusted)		0.030	<0.001	<0.001	0.004
p-value (adjusted)[c]		0.030	<0.001	<0.001	

[a] The assessment made at randomization was considered baseline.
[b] 95% CI of difference corresponds to the unadjusted p-values.
[c] p-values adjusted with Hommel's procedure for multiplicity.
CI Confidence interval. IR Immediate-release. LOCF Last observation carried forward. LS Least squares. MITT Modified intention-to-treat. N Number of patients in treatment group. n Number of patients. NS Not statistically significant. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SE Standard error. SR Sustained-release.
Note: Analysis using analysis of covariance (ANCOVA) with the baseline score as covariate, treatment as fixed effect and center as random effect. Only patients with assessment at baseline and Day 42 (or final assessment) are included.
Note: The IR vs. PLA comparision is included to show assay sensitivity of the study. No multiplicity correction is performed.
Source document: ETI_PANSS_TOT_CHA47.SAS. Generated: 23:04:33 18May2006 DB version prod: 27.

APPENDIX 10.3.5: PANSS TOTAL SCORE, CHANGE FROM BASELINE AT DAY 42 FOR STUDY 132 (OC, MITT POPULATION)

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
n	76	82	91	90	90
Baseline: mean (SD)[a]	97.2 (13.2)	96.0 (13.8)	97.6 (14.1)	96.9 (14.7)	96.2 (16.7)
Day 42: mean (SD)	73.6 (26.1)	65.5 (21.8)	63.3 (18.0)	59.4 (18.6)	63.5 (21.1)
Change from baseline					
LS mean (SE)	-23.1 (2.5)	-31.1 (2.5)	-35.1 (2.3)	-37.7 (2.4)	-33.1 (2.4)
95% CI	-28.0, -18.1	-36.0, -26.3	-39.7, -30.4	-42.4, -33.0	-37.7, -28.4
Difference between active therapy and placebo					
Estimated difference (SE)		-8.1 (2.9)	-12.0 (2.9)	-14.6 (2.9)	-10.0 (2.8)
95% CI[b]		-13.8, -2.4	-17.6, -6.4	-20.3, -9.0	-15.6, -4.4
p-value (unadjusted)		0.006	<0.001	<0.001	<0.001
p-value (adjusted)[c]		0.006	<0.001	<0.001	

[a] The assessment made at randomization was considered baseline.
[b] 95% CI of difference corresponds to the unadjusted p-values.
[c] Interpretation of primary analysis (3 SR groups vs PLA) made with Hommel's procedure for multiplicity. The IR vs. PLA comparision is included to show assay sensitivity of the study. No multiplicity correction is performed.

CI Confidence interval. IR Immediate-release. LS Least squares. MITT Modified intention-to-treat. N Number of patients in treatment group. n Number of patients. OC Observed cases. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SE Standard error. SR Sustained-release.

Note: Analysis using analysis of covariance (ANCOVA) with the baseline score as covariate, treatment as fixed effect and center as random effect. Only patients with assessment at baseline and Day 42 (or final assessment) are included.

Study:D1444C00132, Source document: ETI_PANSS_TOT_CHA_OC48.SAS. Generated: 11:28:03 19May2006 DB version prod: 27.

APPENDIX 10.3.6: LIST OF INVESTIGATORS FOR STUDY 133

Name and Address	Trial No/Center No	Number of patients
Mohammed Bari Synergy Clinical Research Center 1908 Sweetwater Road National City, CA 91950 USA	D1444C00133 Center 0001	12 randomized
Jason Baron MedLabs Research of Houston, Inc. 6260 Westpark Suite 250 Houston, TX 77057 USA	D1444C00133 Center 0002	7 randomized
Ronald Brenner Neurobehavioral Research, Inc. Department of Psychiatry, 5th Floor 371 Central Avenue Lawrence, NY 11559 USA	D1444C00133 Center 0004	9 randomized
David Brown Community Clinical Research, Inc. 4411 Medical Parkway Austin, TX 78756 USA	D1444C00133 Center 0005	15 randomized

Name and Address	Trial No/Center No	Number of patients
Robert Dahmes Louisiana Research Associates 3520 General DeGaulle Drive #4030 New Orleans, LA 70114 USA	D1444C00133 Center 0006	16 randomized
Himasiri De Silva Clinical Innovations 801 N. Tustin Avenue Suite 600 Santa Ana, CA 92705 USA	D1444C00133 Center 0007	30 randomized
Juan Espinosa TuKoi Institute for Clinical Research 20820 West Dixie Highway Miami, FL 33180 USA	D1444C00133 Center 0008	10 randomized
Carlos Figueroa Advanced Psychiatric Group 180 North San Gabriel Boulevard Pasadena, CA 91107 USA	D1444C00133 Center 0010	17 randomized
Donald Garcia FutureSearch Trials 4200 Marathon Blvd. Suite 200 Austin, TX 78756 USA	D1444C00133 Center 0011	16 randomized
John Gilliam International Clinical Research Associates, LLC 1601 Rolling Hills Drive Suite 201 Richmond, VA 23229 USA	D1444C00133 Center 0012	4 randomized
Richard Josiassen Arthur P. Noyes Research Foundation 001 Sterigere Street Norristown, PA 19401 USA	D1444C00133 Center 0014	1 randomized

Name and Address	Trial No/Center No	Number of patients
Mary Knesevich University Hills Clinical Research 102 Decker Drive Suite 250 Irving, TX 75062 USA	D1444C00133 Center 0015	20 randomized
James Knutson Eastside Therapeutic Resource 512 6th Street Suite 101 Kirkland, WA 98033 USA	D1444C00133 Center 0016	10 randomized
Joseph Kwentus University of Mississippi Medical Center Department of Psychiatry 2500 North State Street Campus Box 138 Jackson, MS 39216 USA	D1444C00133 Center 0017	9 randomized
David Linden Linden Research Consultants, LLC 5801 North Broadway Extension Suite 401 Oklahoma City, OK 73118 USA	D1444C00133 Center 0018	1 randomized
Robert Litman CBH Health, LLC 2960 Sleepy Hollow Road 3 South Fall Church, VA 22044 USA	D1444C00133/0019	16 randomized
Edward Logue Birmingham Psychiatry Pharmaceutical Studies, Inc. 100 Century Park South Suite 214 Birmingham, AL 35226 USA	D1444C00133 Center 0020	10 randomized

Name and Address	Trial No/Center No	Number of patients
Raymond Manning California Neuropsychopharmacology Clinical Research Institute 8309 Telegraph Road Pico Rivera, CA 90660 USA	D1444C00133 Center 0021	27 randomized
Michael Plopper Sharp Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123 USA	D1444C00133 Center 0022	10 randomized
David Sack Comprehensive Neuroscience, Inc. 11808 E. Artesia Blvd. Suite A Cerritos, CA 90703 USA	D1444C00133 Center 0024	18 randomized
Stephen Saklad University of Texas Health Science Center at San Antonio Psychiatry 7703 Floyd Curl Drive San Antonio, TX 78284	D1444C00133 Center 0025	2 randomized
Adam Sky Sky, LLC 103 Bellevue Avenue Suite 412 St. Louis, MO 63117	D1444C00133 Center 0026	3 randomized
Tram Tran-Johnson CNRI-San Diego LLC 9466 Black Mountain Road Suite 100 San Diego, CA 92126 USA	D1444C00133 Center 0028	31 randomized
Madeleine Valencerina Kedren Community Mental Health Center 10802 College Place Cerritos, CA 90703 USA	D1444C00133 Center 0029	9 randomized

Name and Address	Trial No/Center No	Number of patients
Joseph Fanelli Midwest Center for Neurobehavioral Medicine 18 W. 100 22nd Street Suite 126 Oakbrook Terrace, IL 60181 USA	D1444C00133 Center 0031	0 Randomized
Rakesh Ranjan Rakesh Ranjan, MD & Associates 5010 Mayfield Road Suite 309 Lyndhurst, OH 44124 USA	D1444C00133 Center 0032	1 randomized
Stephen Peterson Washington Hospital Center 110 Irving Street NW EB Room 4129 Washington, DC 20010 USA	D1444C00133 Center 0033	31 randomized
Michael Levy Behavioral Medical Research of Staten Island 500 Seaview Avenue Suite 200 Staten Island, NY 10305 USA	D1444C00133 Center 0034	9 randomized
William Fuller Avera Research Institute 2020 South Norton Avenue Sioux Falls, SD 57105 USA	D1444C00133 Center 0035	0 randomized
Jeffrey Borenstein The Holliswood Hospital 87-37 Palermo Street Holliswood, NY 11423 USA	D1444C00133 Center 0037	6 randomized
Richard Jaffe Belmont Center for Comprehensive Treatment 4200 Monument Road Philadelphia, PA 19131 USA	D1444C00133 Center 0038	22 randomized

Name and Address	Trial No/Center No	Number of patients
Adam Lowy Comprehensive Neuroscience, Inc. 4228 Wisconsin Avenue NW Washington, DC 20016 USA	D1444C00133 Center 0039	24 randomized
Arthur Freeman University of Tennessee Department of Psychiatry 135 North Pauline Memphis, TN 38105 USA	D1444C00133 Center 0040	3 randomized
Andrew Cutler Florida Clinical Research Center, LLC 2020 26th Avenue East Bradenton, FL 34208 USA	D1444C00133 Center 0041	6 randomized
Steven Glass CNS Research Institute (CRI) 130 White Horse Pike Clementon, NJ 08021 USA	D1444C00133 Center 0042	25 randomized
Mark Lerman Alexian Brothers Behavioral Health Hospital 1650 Moon Lake Blvd Hoffman Estates, IL 60194 USA	D1444C00133 Center 0043	8 randomized
Stephen Mohaupt California Clinical Trials 15625 Lakewood Blvd Paramount, CA 90723 USA	D1444C00133 Center 0044	34 randomized
Murray Rosenthal California Clinical Trials 3625 Ruffin Road, Suite 100 San Diego, CA 92123 USA	D1444C00133 Center 0045	17 randomized
Scott Aaronson Sheppard Pratt Health System 6501 N. Charles Street Baltimore, MD 21204 USA	D1444C00133 Center 0046	0 randomized

Name and Address	Trial No/Center No	Number of patients
Carlos Collin CBH Health, LLC Fellowship House 707 St. Paul Street Baltimore, MD 21202 USA	D1444C00133 Center 0047	27 randomized
Raj Rajani California Clinical Trials Behavioral & Research Medicine, LLC 1000 South Anaheim Blvd. Suite 204 Anaheim, CA 92805 USA	D1444C00133 Center 0048	14 randomized
Rajinder Shiwach InSite Clinical Research 2000N. Old Hickory Trail DeSoto, TX 75115 USA	D1444C00133 Center 0050	16 randomized
Joachim Raese Behavioral Health 2000, LLC 5945 Brockton Avenue Riverside, CA 92506 USA	D1444C00133 Center 0051	0 randomized
David Walling Collaborative Neuroscience Network 12772 Valley View Street Suite 3 Garden Grove, CA 92845 USA	D1444C00133 Center 0052	19 randomized

APPENDIX 10.3.7: PANSS TOTAL SCORE, CHANGE FROM BASELINE AT DAY 42 FOR STUDY 133 (LOCF, MITT POPULATION)

	PLA N=111	QTP SR 400 mg N=113	QTP SR 600 mg N=101	QTP SR 800 mg N=110	QTP IR 800 mg N=109
n	111	113	101	110	109
Baseline: mean (SD)[a]	90.8 (11.9)	91.1 (13.4)	93.1 (14.0)	92.6 (13.2)	93.0 (13.5)
Day 42: mean (SD)	79.9 (21.1)	78.6 (18.7)	77.0 (18.6)	78.5 (20.4)	78.5 (19.6)
Change from baseline					
LS mean (SE)	-12.1 (1.9)	-13.8 (1.9)	-16.8 (2.0)	-14.8 (1.9)	-15.0 (1.9)
95% CI	-15.8, -8.4	-17.5, -10.1	-20.7, -13.0	-18.5, -11.1	-18.8, -11.3
Difference between active therapy and placebo					
Estimated difference (SE)		-1.7 (2.2)	-4.7 (2.2)	-2.7 (2.2)	-3.0 (2.2)
95% CI[b]		-5.9, 2.5	-9.1, -0.4	-7.0, 1.6	-7.3, 1.3
p-value (unadjusted)		0.434	0.033	0.214	0.172
p-value (adjusted)[c]		0.434	0.099	0.429	

[a] The assessment made at randomization was considered baseline.
[b] 95% CI of difference corresponds to the unadjusted p-values.
[c] p-values adjusted with Hommel's procedure for multiplicity.

CI Confidence interval. IR Immediate-release. LOCF Last observation carried forward. LS Least squares. MITT Modified intention-to-treat. N Number of patients in treatment group. n Number of patients. NS Not statistically significant. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SE Standard error. SR Sustained-release.

Note: Analysis using analysis of covariance (ANCOVA) with the baseline score as covariate, treatment as fixed effect and center as random effect. Only patients with assessment at baseline and Day 42 (or final assessment) are included.

Note: The IR vs. PLA comparision is included to show assay sensitivity of the study. No multiplicity correction is performed.

Source document: ETI_PANSS_TOT_CHA47.SAS. Generated: 10:00:47 22May2006 DB version prod: 24.

APPENDIX 10.3.8: LIST OF INVESTIGATORS FOR STUDY 041

Name and Address	Trial No/Center No	Number of patients
George Ainslie, MD Department of Veteran Affairs Medical Center Psychiatry (116A) Building 38 1400 Black Horse Hill Road Coatesville PA 19320	5077IL0041 Center 01	1 randomized
Fred Stoddard MD California Clinical Studies, LLC 532 Oregon Street Vallejo, CA 94590	5077IL0041 Center 02	No enrollment occurred at this center
Mark Randall Bloch MD Affiliated Research Institute 2850 Telegraph Avenue Suite 125 Berkeley, CA 94705	5077IL0041 Center 03	3 randomized
Sajal Bose MD Behavioral Heathcare Corp. BHC Valle Vista Health System, 898 East Main Street, Greenwood, IN 46143	5077IL0041 Center 04	8 randomized
David Brown MD Community Clinical Research Inc. 4411 Medical parkway Austin TX 78756	5077IL0041 Center 05	37 randomized
John Carman MD Carman Research 4015 South Cobb Drive Suite 245 Smyrna, GA 30080	5077IL0041 Center 06	No enrollment occurred at this center

Name and Address	Trial No/Center No	Number of patients
James C Y Chou. MD New York University Medical Center, Bellevue Hospital Center Department of Psychiatry Room 20 West 13A462 1st Avenue New York NY 10016	5077IL0041 Center 07	2 randomized
Evangelos Coskinas MD (2/20/01 to 10/16/01) Affiliated Research Institute 801 North Tustin Avenue Suite 600 Santa Ana, CA 92705 Himasiri DeSilva MD (10/17/01 to end of study)	5077IL0041 Center 08	9 randomized
Murray Rosenthal MD Behavioral and Medical Research 3625 Ruffin Road Suite 100 San Diego, CA 92123	5077IL0041 Center 09	25 randomized
Andrew Cutler MD CORE Research Inc 807 West Morse Boulevard Suite 101 Winter Park FL 32789	5077IL0041 Center 10	34 randomized
Robert Diamond MD (2/20/01 to 3/26/01) BHC Sierra Vista Hospital 8001 Bruceville Road Sacramento CA 95823 Dennis Twigg MD (3/27/01 to end of study)	5077IL0041 Center 11	No enrollment occurred at this center
Bradley Diner MD Arkansas Psychiatric Clinic 5 St. Vincent Circle Suite 301 Little Rock, AK 72205	5077IL0041 Center 12	9 randomized

Name and Address	Trial No/Center No	Number of patients
Eduardo Dunayevich, MD (2/20/01 to 8/1/01) University of Cincinnati College of Medicine Department of Psychiatry 231 Bethesda Avenue Cincinnati OH 45267-0559 Stephen Strakowski MD (8/2/01 to end of study)	5077IL0041 Center 13	8 randomized
Steven Eisen MD ICSL- Clinical Studies 400 Market Street Suite 425 Philadelphia PA 19106	5077IL0041 Center 14	6 randomized
Louis Fabre MD Fabre Research Clinic Inc. 5503 Crawford Street Houston, TX 77004	5077IL0041 Center 15	21 randomized
William Fuller MD Health Science Center University Physicians 1400 West 22nd Street Room 308 Sioux Falls SD 57105	5077IL0041 Center 16	7 randomized
David Garver MD University of Louisville Department of Psychiatry and Behavioral Sciences 500 South Preston Street Building A, Room 210 Louisville, KY 40202	5077IL0041 Center 17	3 randomized
Clifford Goldman MD ClinSearch Inc 1700 Galloping Hill Road Kennilworth, NJ 07033	5077IL0041 Center 18	1 randomized
Mark Hamner MD Medical University of South Carolina Ralph H. Johnson VA Medical Center Department of Psychiatry 16A 109 Bee Street Charleston SC 29401	5077IL0041 Center 19	No enrollment occurred at this center

Name and Address	Trial No/Center No	Number of patients
Scott Hoopes MD Mountain West Clinical Trials LLC 315 North Allumbaugh Boise ID 83704 - 9208	5077IL0041 Center 20	1 randomized
Saleem Ishaque MD Synergy Clinical Research Center 450 Fourth Avenue Suite 409 Chula Vista CA 91910	5077IL0041 Center 21	42 randomized
Alan Jonas MD PharmaSite Research Inc 1314 Bedford Avenue Suite 205 Baltimore MD 21208	5077IL0041 Center 22	No enrollment occurred at this center
Arif Khan MD (2/20/01 to 5/16/01) BHC Fairfax Hospital 10200 NE 132nd Street Kirkland WA 98034 James Knutson MD (5/17/01 to end of study)	5077IL0041 Center 23	13 randomized
Michael Levy MD Staten Island University Hospital 450 Seaview Avenue Staten Island, NY 10305	5077IL0041 Center 24	5 randomized
John Kasckow MD Cincinnati Veterans Affairs Medical Center 3200 Vine Street Cincinnati OH 45220	5077IL0041 Center 25	10 randomized
Mary Ann Knesevich MD 5959 Harry Hines Boulevard Suite 924 Dallas TX 75235	5077IL0041 Center 26	33 randomized
Michael Lesem MD Claghorn-Lesem Research Clinic 6750 West Loop South Suite 1050 Bellaire TX 77401	5077IL0041 Center 27	24 randomized

Name and Address	Trial No/Center No	Number of patients
Jean Pierre Lindenmayer MD Psychopharmacology Research Program Manhattan Psychiatric Center Wards Island Complex New York NY 10035	5077IL0041 Center 28	4 randomized
Paul Markovitz MD PhD 7409 North Cedar Avenue Suite 101 Fresno CA 93720	5077IL0041 Center 29	1 randomized
Howard Mason MD BHC Montevista Hospital 5900 West Rochelle Avenue Las Vegas NV 89103	5077IL0041 Center 30	1 randomized
Denis Mee-Lee MD Hawaii Clinical Research Center 1750 Kalakaua Avenue Suite 2602 Honolulu HI 96826	5077IL0041 Center 31	8 randomized
Charles Merideth, MD Affiliated Research Institute 8989 Rio San Diego Drive Suite 350 San Diego CA 92108	5077IL0041 Center 32	26 randomized
Alexander Miller MD University of Texas Health Sciences Center Department of Psychiatry Mail Stop 7792 7703 Floyd Curl Drive San Antonio TX 78229-3900	5077IL0041 Center 33	16 randomized
Henry Nasrallah MD 1500 East Woodrow Wilson Drive Jackson MS 39216	5077IL0041 Center 34	No enrollment occurred at this center
Michael Plopper MD Sharp Mesa Vista Hospital 7850 Vista Hill Avenue San Diego CA 92123	5077IL0041 Center 35	17 randomized
Steven Potkin MD University of California Irvine Medical Center 101 City Drive South Orange CA 92868	5077IL0041 Center 36	20 randomized

Name and Address	Trial No/Center No	Number of patients
Rakesh Ranjan MD Rakesh Ranjan, MD & Associates Inc 600 East Smith Road Suite H Medina OH 44256	5077IL0041 Center 38	6 randomized
Raj Rajani MD Behavioral and Medical Research, LLC 1000 South Anaheim Boulevard Suite 204 Anaheim CA 92805	5077IL0041 Center 39	19 randomized
Craig Risch MD Medical University of South Carolina (MUSC) Institute of Psychiatry Clinical Neuropharmacology 61 President Street 4 South PO Box 250861 Charleston SC 29425	5077IL0041 Center 40	4 randomized
Charles Schulz MD (2/20/01 to 5/13/01) University Of Minnesota Medical School Department of Psychiatry 2450 Riverside Avenue F282/2A West Building Minneapolis MN 55454 Stephen Olson MD (5/14/01 to end of study)	5077IL0041 Center 42	No enrollment occurred at this center
Kenneth Sokolski MD (2/20/01 to 2/20/02) Advanced Behavioral Research Institute 1735 West Romneya Drive Anaheim CA 92801 Bum Soo Lee MD (2/21/02 to end of study)	5077IL0041 Center 43	22 randomized
Kathleen Toups MD Bay Area Research Institute 2123 Ygnacio Valley Road Suite K200 Walnut Creek CA 94598	5077IL0041 Center 44	1 randomized

Name and Address	Trial No/Center No	Number of patients
Kenneth Weiss MD Delaware Valley Research Associates Inc 922 Fayette Street Conshohocken, PA 19428	5077IL0041 Center 45	4 randomized
Daniel Anderson MD Affiliated Research Institute 3490 Linden Avenue Suite 1 Long Beach CA 90807	5077IL0041 Center 46	9 randomized
Ronald Brenner MD Neurobehavioral Research Inc. 371 Central Avenue Lawrence NY 11559	5077IL0041 Center 47	17 randomized
William Privitera MD Future Search Trials 4200 Marathon Boulevard #200 Austin, TX 78756	5077IL0041 Center 49	10 randomized
Kevin Caputo MD Crozer Chester Medical Center Office of Clinical Research One Medical Center Boulevard Upland PA 19013	5077IL0041 Center 50	3 randomized
Siemion Altman MD Riverview Hospital 500 Lougheed Hghway Port Coquitlam BC V3C 4J2	5077IL0041 Center 51	2 randomized
Denis Cliché MD Les Fonds D.S.1515-17 Rue St. George, Beauce PQ G5Y 4T8	5077IL0041 Center 52	8 randomized
Wilson Lit MD Homewood Health Centre 150 Delhi Street Guelph, Ont. N1E 6K9	5077IL0041 Center 53	No enrollment occurred at this center
Richard Williams MD Eric Martin Pavilion Royal Jubilee Hospital 2334 Trent St. Victoria, BC V8R 4Z3	5077IL0041 Center 54	No enrollment occurred at this center

Name and Address	Trial No/Center No	Number of patients
Alain Labelle MD University of OttawaRoyal Ottawa Hospital 1145 Carling Ave. Ottawa, Ont. K1Z 7K4	5077IL0041 Center 57	6 randomized
Jeffrey Reiss MD Psychiatry Health Centre 771 Bannatyne Ave. Winnipeg, Ont. R3E 3N4	5077IL0041 Center 58	2 randomized
S. Reddy Pasem MD Magnolia Research Group Inc. 2203 Southeast Third Avenue Ocala, FL 34471	5077IL0041 Center 59	1 randomized
David Sack MD Comprehensive NeuroSience 11050 Artesia Boulevard Suite G Cerritos CA 90703	5077IL0041 Center 60	10 randomized
Robert Riesenberg MD Atlanta Center for Medical Research 811 Juniper Street NE Atlanta GA 30308	5077IL0041 Center 61	4 randomized
Adam Lowy MD Comprehensive Neuroscience Inc 4228 Wisconsin Avenue NW Washington DC 20016	5077IL0041 Center 62	8 randomized
Jason Baron MD Med Labs Research of Houston Inc. 6260 Westpark Suite 150 Houston, TX 77057	5077IL0041 Center 63	No enrollment occurred at this center
Mark Lerman MD Comprehensive NeuroScience Inc 1650 Moon Lake Boulevard Hoffman Estates IL 60194	5077IL0041 Center 64	2 randomized
Georgina del Carmen Herrera, MD BHC Mesilla Valley Hospital 3751 Del Ray Blvd, Las Cruces, NM 88012	5077IL0041 Center 66	No enrollment occurred at this center

APPENDIX 10.3.9: PANSS TOTAL SCORE, CHANGE FROM BASELINE AT DAY 42 FOR STUDY 041 (LOCF, MITT POPULATION)

Summary statistic	Placebo (n=78)	QTP SR 300 mg (n=83)	QTP SR 600 mg (n=87)	QTP SR 800 mg (n=85)	QTP IR 300 mg (n=85)	QTP IR 600 mg (n=80)
PANSS total score, LSmean change from BL[a]	-5.19	-5.01	-13.01[b]	-11.17	-9.42	-6.97
PANSS response, % patients with ≥30% improvement[c]	14.1	12.0	24.1	23.5	18.8	13.8
CGI Severity of Illness score, LSmean change from BL	–0.42	–0.50	–0.66	–0.68	–0.59	–0.51
CGI Global Improvement, % patients with improvement[d]	48.7	50.6	64.4	55.3	57.6	53.8
% much/very much improved	19.2	30.1	33.3	35.3[e]	42.3[e]	26.3

[a] Mean baseline PANSS total scores across treatment groups were 91.1, 91.5, 92.4, 89.0, 89.5, and 88.6, respectively.
[b] Significantly different versus placebo (analysis of covariance adjusted for multiplicity, p=0.033)
[c] In PANSS total score.
[d] Includes patients improved, much improved and minimally improved per CGI Global Improvement rating.
[e] Significantly different from placebo (Cochran-Mantel-Haenszel analysis, p=0.015 for SR 800 mg and 0.005 for IR 300 mg).

BL Baseline. CGI Clinical Global Impression. LOCF Last observation carried forward. LSmean Least-squares mean.
MITT Modified intent-to-treat. PANSS Positive and Negative Syndrome Scale.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.
Data derived from Tables 11.2.1.1.1, 11.2.1.2.7, 11.2.2.1.5, 11.2.2.2.1, 11.2.2.3.3, 11.2.2.3.5.3, and 11.2.2.3.6, Section 11.2.

10.4 Appendix to Integrated Review of Efficacy (Section 6)

APPENDIX 10.4.1.1: PRIMARY EFFICACY VARIABLE PANSS TOTAL SCORE BY AGE GROUP; CHANGE FROM BASELINE AT DAY 42 FOR STUDY 132 (LOCF, MITT POPULATION)

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
18 to 39 years					
n	84	78	81	76	83
Baseline: mean (SD)	96.8 (13.7)	95.4 (14.8)	96.6 (13.3)	95.9 (15.2)	97.3 (16.2)
Day 42: mean (SD)	78.7 (27.3)	69.7 (22.8)	65.7 (18.8)	66.8 (25.1)	70.9 (27.1)
Change from baseline					
LS mean (SE)	-17.8 (2.8)	-26.3 (2.9)	-30.5 (2.8)	-29.2 (2.9)	-26.0 (2.8)
95% CI	-23.3, -12.3	-32.1, -20.6	-36.1, -24.8	-34.9, -23.5	-31.5, -20.5
Difference between active therapy and placebo					
Estimated difference (SE)		-8.5 (3.4)	-12.7 (3.4)	-11.4 (3.4)	-8.2 (3.3)
95% CI		-15.2, -1.9	-19.3, -6.0	-18.1, -4.6	-14.8, -1.7
40 to 65 years					
n	31	33	30	41	36
Baseline: mean (SD)	94.8 (12.2)	96.8 (11.6)	97.5 (16.4)	100.0 (13.6)	94.6 (15.5)
Day 42: mean (SD)	76.8 (19.7)	76.2 (27.0)	70.3 (24.2)	64.5 (21.9)	68.6 (24.7)
Change from baseline					
LS mean (SE)	-18.9 (4.0)	-20.0 (3.9)	-29.3 (4.1)	-34.1 (3.6)	-26.5 (3.8)
95% CI	-26.8, -11.0	-27.7, -12.2	-37.4, -21.1	-41.3, -26.9	-34.1, -19.0
Difference between active therapy and placebo					
Estimated difference (SE)		-1.0 (5.2)	-10.4 (5.3)	-15.2 (5.0)	-7.6 (5.1)
95% CI		-11.2, 9.2	-20.9, 0.2	-25.1, -5.2	-17.8, 2.5

APPENDIX 10.4.1.2: PRIMARY EFFICACY VARIABLE PANSS TOTAL SCORE BY GENDER; CHANGE FROM BASELINE AT DAY 42 FOR STUDY 132 (LOCF, MITT POPULATION)

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
Male					
n	67	78	61	70	69
Baseline: mean (SD)	95.6 (12.2)	96.3 (14.0)	99.5 (14.2)	98.6 (14.9)	97.8 (16.9)
Day 42: mean (SD)	76.0 (26.3)	73.7 (25.8)	66.9 (20.5)	69.3 (24.9)	67.0 (24.4)
Change from baseline					
LS mean (SE)	-19.2 (3.1)	-23.0 (2.9)	-31.5 (3.2)	-28.2 (3.0)	-29.7 (3.1)
95% CI	-25.2, -13.1	-28.8, -17.1	-37.8, -25.1	-34.2, -22.2	-35.8, -23.7
Difference between active therapy and placebo					
Estimated difference (SE)		-3.8 (3.7)	-12.3 (3.9)	-9.1 (3.8)	-10.6 (3.8)
95% CI		-11.1, 3.5	-20.0, -4.6	-16.5, -1.6	-18.0, -3.2
Female					
n	48	33	50	47	50
Baseline: mean (SD)	97.1 (14.8)	94.6 (13.8)	93.5 (13.4)	95.4 (14.5)	94.8 (14.7)
Day 42: mean (SD)	81.3 (23.9)	66.6 (19.1)	66.9 (20.6)	61.1 (21.9)	74.6 (28.5)
Change from baseline					
LS mean (SE)	-17.9 (3.4)	-27.1 (3.8)	-29.7 (3.3)	-34.2 (3.4)	-21.4 (3.3)
95% CI	-24.7, -11.2	-34.7, -19.5	-36.2, -23.1	-40.8, -27.5	-27.9, -15.0
Difference between active therapy and placebo					
Estimated difference (SE)		-9.2 (4.4)	-11.7 (3.9)	-16.2 (4.0)	-3.5 (3.9)
95% CI		-17.9, -0.4	-19.5, -4.0	-24.2, -8.3	-11.2, 4.3

IR Immediate release. LOCF Last observation carried forward. LS Least squares. MITT Modified intent-to-treat. N Number of patients in treatment group. n Number of patients. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine.
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APPENDIX 10.4.1.3: PRIMARY EFFICACY VARIABLE PANSS TOTAL SCORE BY RACE; CHANGE FROM BASELINE AT DAY 42 FOR STUDY 132 (LOCF, MITT POPULATION)

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
Caucasian					
n	68	63	66	71	71
Baseline: mean (SD)	95.6 (12.4)	95.9 (13.2)	96.3 (13.6)	96.5 (13.5)	95.6 (15.5)
Day 42: mean (SD)	77.4 (22.3)	72.8 (24.2)	69.3 (21.4)	66.4 (22.1)	70.9 (24.7)
Change from baseline					
LS mean (SE)	-19.3 (3.0)	-23.8 (3.1)	-28.3 (3.0)	-30.0 (3.0)	-24.8 (2.9)
95% CI	-25.2, -13.4	-29.8, -17.7	-34.2, -22.3	-35.9, -24.2	-30.7, -19.0
Difference between active therapy and placebo					
Estimated difference (SE)		-4.5 (3.3)	-9.0 (3.3)	-10.7 (3.2)	-5.6 (3.2)
95% CI		-10.9, 2.0	-15.4, -2.6	-17.1, -4.4	-11.8, 0.7
Black					
n	5	5	4	5	7
Baseline: mean (SD)	89.2 (10.7)	91.0 (12.5)	86.3 (12.7)	96.0 (5.2)	95.0 (9.5)
Day 42: mean (SD)	55.6 (20.3)	55.8 (17.6)	55.0 (15.8)	60.2 (9.8)	61.0 (27.4)
Change from baseline					
LS mean (SE)	-32.4 (10.5)	-30.6 (10.9)	-30.4 (11.1)	-34.7 (10.2)	-33.3 (8.5)
95% CI	-54.8, -9.9	-53.8, -7.3	-53.6, -7.1	-56.5, -12.9	-51.7, -15.0
Difference between active therapy and placebo					
Estimated difference (SE)		1.8 (13.2)	2.0 (14.0)	-2.4 (12.9)	-1.0 (12.0)
95% CI		-25.8, 29.4	-27.2, 31.2	-29.6, 24.8	-26.3, 24.3
Oriental					
n	42	43	40	41	41
Baseline: mean (SD)	98.1 (14.8)	96.3 (15.2)	98.8 (15.0)	98.9 (17.4)	98.4 (17.8)
Day 42: mean (SD)	82.1 (29.4)	71.7 (24.6)	64.4 (19.1)	66.0 (28.3)	70.6 (29.2)
Change from baseline					
LS mean (SE)	-15.6 (4.6)	-24.9 (4.6)	-33.9 (4.8)	-32.0 (4.7)	-27.5 (4.7)
95% CI	-25.2, -5.9	-34.5, -15.3	-43.9, -24.0	-41.6, -22.3	-37.3, -17.6
Difference between active therapy and placebo					
Estimated difference (SE)		-9.4 (5.3)	-18.4 (5.4)	-16.4 (5.4)	-11.9 (5.3)
95% CI		-19.7, 1.0	-29.0, -7.8	-27.0, -5.9	-22.4, -1.4
Other					
n	0	0	1	0	0

Baseline: mean (SD)	96.0
Day 42: mean (SD)	61.0
Change from baseline	
LS mean (SE)	
95% CI	
Difference between active therapy and placebo	
Estimated difference (SE)	
95% CI	

IR Immediate release. LOCF Last observation carried forward. LS Least squares. MITT Modified intent-to-treat. N Number of patients in treatment group. n Number of patients. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine.
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/s/

Michelle Chuen
4/9/2007 04:03:09 PM
MEDICAL OFFICER

Greg Dubitsky
4/9/2007 04:57:04 PM
MEDICAL OFFICER

Ni Aye Khin
4/24/2007 06:06:57 PM
MEDICAL OFFICER
I agree that this NDA be considered for an approvable action; see also memo to file for additional comments.